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Predictors of urinary polycyclic aromatic hydrocarbon metabolites in girls from the San Francisco Bay Area

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Declaration of competing interests

The authors declare no conflict of interest related to this work.

Appendix A. Supplementary material

Abstract

Background: Polycyclic aromatic hydrocarbon (PAH) exposures from tobacco smoke, automobile exhaust, grilled or smoked meat and other sources are widespread and are a public health concern, as many are classified as probable carcinogens and suspected endocrine-disrupting chemicals. PAH exposures can be quantified using urinary biomarkers.

Methods: Seven urinary metabolites of naphthalene, fluorene, phenanthrene, and pyrene were measured in two samples collected from girls aged 6–16 years from the San Francisco Bay Area. We used Spearman correlation coefficients (SCC) to assess correlations among metabolite concentrations (corrected for specific gravity) separately in first (n=359) and last (N=349) samples, and to assess consistency of measurements in samples collected up to 72 months apart. Using multivariable linear regression, we assessed variation in mean metabolites across categories of participant characteristics and potential outdoor, indoor, and dietary sources of PAH exposures.

Results: The detection rate of PAH metabolites was high (4 metabolites in ≥98% of first samples; 5 metabolites in ≥95% of last samples). Correlations were moderate to strong between fluorene, phenanthrene and pyrene metabolites (SCC 0.43–0.82), but weaker between naphthalene and the other metabolites (SCC 0.18–0.36). SCC between metabolites in first and last samples ranged from 0.15–0.49. When classifying metabolite concentrations into tertiles based on single samples (first or last samples) vs. the average of the two samples, agreement was moderate to substantial (weighted kappa statistics 0.52–0.65). For specific metabolites, concentrations varied by age, race/ethnicity, and body mass index percentile, as well as by outdoor sources (season of sample collection, street traffic), indoor sources (heating with gas, cigarette smoke), and dietary sources (frequent use of grill, consumption of smoked meat or fish) of PAH exposures.

Conclusions: Urinary PAH exposure was widespread in girls aged 6–16 years and associated with several sources of exposure. Tertile classification of a single urine sample provides reliable PAH exposure ranking.

Keywords

biomarkers; children; epidemiology; polycyclic aromatic hydrocarbons (PAHs); urinary metabolites

1. Introduction

Exposures to environmental chemicals are widespread in the United States (U.S.) (CDC, 2021) including polycyclic aromatic hydrocarbons (PAHs) that are formed during incomplete combustion of organic materials. People are commonly exposed to multiple sources of PAHs and mixtures of PAHs, including tobacco smoke, automobile exhaust, and charred meat grilled at high temperature (ATSDR, 2009). Through metabolic biotransformation of PAHs, hydroxylated metabolites are generated, which are excreted in urine (Ramesh et al., 2004). Urinary PAH metabolites capture exposure from multiple sources and are used as biomarkers of PAH exposure in biomonitoring programs in the U.S. (CDC, 2021; Grainger et al., 2006; Li et al., 2008) and elsewhere (Murawski et al., 2020). In the U.S., PAH metabolites are detectable in 96% of the non-smoking population, including children (Grainger et al., 2006; Huang et al., 2006; Hudson-Hanley et al., 2021).

Many PAHs are classified as probable human carcinogens (IARC, 2010) and are suspected endocrine-disrupting chemicals that have been associated with effects on pubertal development in animal studies (Schug et al., 2011), reproductive hormone disruption in women (Luderer et al., 2017), and increased risk of breast cancer (White et al., 2016; Bonner et al., 2005; Nie et al., 2007; White et al., 2014; Shmuel et al., 2017; Niehoff et al., 2017; Rodgers et al., 2018). Investigation of the effects of PAHs on pubertal development is highly relevant to breast cancer, as milestones of pubertal development, such as younger ages at menarche and onset of breast development, are associated with increased breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Bodicoat et al., 2014; Goldberg et al., 2020). We conducted a study in the California cohort of the Lessons in Epidemiology and Genetics and Adult Cancer from Youth (LEGACY) Girls Study (John et al., 2016) to examine the relation between pubertal timing and urinary metabolites of four PAHs (naphthalene, fluorene, phenanthrene, and pyrene) that are classified as priority pollutants by the Environmental Protection Agency (OFR, 1982). In this first report, we examined variation in urinary PAH metabolites in girls aged 6–16 years, correlations between metabolites, and variation in metabolites by participant and sample collection characteristics and outdoor, indoor, and dietary sources of PAH exposure assessed by questionnaire.

2. Materials and methods

The study is based on the LEGACY Girls Study, a multi-center prospective cohort conducted from 2011–2016 (John et al., 2016). The California site enrolled 362 girls aged 6–16 years and their mothers from the San Francisco Bay Area. Of these participants, 251 girls and their mothers enrolled in the California PAH Study (2017–2020).

2.1. Study sample

The study sample included 359 girls who provided a urine sample at enrollment in the LEGACY Girls Study. The Institutional Review Boards of the Cancer Prevention Institute of California and Stanford University and the California Committee for the Protection of Human Subjects approved both studies.

2.2. Urine and data collection

First-void morning urine samples were collected at enrollment and each follow-up visit in the LEGACY Girls Study and at enrollment in the California PAH Study. Of 359 study participants, 349 (99%) provided additional urine samples during follow-up (total of 2,164 samples) or at enrollment in the California PAH Study (191 samples). For both studies, urine samples were collected in the morning of the study visit using a mailed self-collection kit, transferred to the lab, aliquoted within 48 hours of collection, and stored in −80° C freezers.

At enrollment in the LEGACY Girls Study, participating mothers completed a baseline questionnaire on the girls' sociodemographic background, family history of breast cancer, medical history, and pubertal development, and trained staff measured the girls' weight and height (two measurements each) using a digital scale and stadiometer, respectively (John et al., 2016). At enrollment in the California PAH Study, mothers completed a questionnaire

on the girls' lifetime residential history and potential sources of PAH exposure, girls of all ages participated in weight and height measurements, and girls aged ≥10 years completed questions on select sources of PAH exposure.

2.3. Measurement of urinary PAH metabolites

Seven urinary PAH metabolites were measured including 1-hydroxy naphthalene (1-NAP), 2-hydroxy naphthalene (2-NAP), 2- and 3-hydroxy fluorene (2&3-FLU), 1-hydroxy phenanthrene (1-PHEN), 2- and 3-hydroxy phenanthrene (2&3-PHEN), 4-hydroxy phenanthrene (4-PHEN), and 1-hydroxy pyrene (1-PYR). Specific gravity (SG) was measured to account for urine dilution. SG and PAH metabolites were measured in 359 first samples and 349 last samples from the same girls. Since not all girls participated in the California PAH Study, the last sample came from the LEGACY Girls Study for 158 girls and from the California PAH Study for 191 girls. The mean time between the first and last sample was 45 months (median 54 months, range 6–72 months). For a subset of 72 girls, PAH metabolites were measured in a third sample that was collected when breast composition was measured during follow-up of the LEGACY Girls Study.

SG was measured using an Atago PAL-10-S refractometer. Optima LC/MS grade water and synthetic urine were used to check the performance of the refractometer before daily usage and in between sets of seven samples. Urinary PAH metabolites were measured using the method described elsewhere (Nguyen et al., 2021; under review). Briefly, 1mL urine samples were thawed and internal standards were added prior to adding 1mL β-glucuronidase/aryl sulfatase H1 enzyme solution (10mg/ml in 0.1M sodium acetate, pH 5.5). The mixture was incubated for 17–18 hours in a water bath at 37°C. The hydrolyzed samples were diluted with 15% methanol in sodium acetate (0.1M, pH 5.5) prior to solid phase extraction. The analytes of interest were extracted by using Bond Elut Focus 60mg, 3ml cartridges (Agilent) as follows: the cartridges were conditioned with 1ml of optimal grade water, equilibrated with 1ml of optimal methanol. Diluted samples were loaded at a flow rate of 1ml/min. Subsequently, the cartridges were rinsed with 1ml of water followed by 3ml of 70:30 sodium acetate methanol mixture, then were blown dry under air purging and nitrogen flow of 2ml/min for 10 minutes. Finally, the samples were eluted using 6ml of optimal grade methanol and concentrated using Turbo-Vap with gentle flow of nitrogen (2–4 psi). The analytes were then reconstituted in methanol to the final volume of 150–300 ul for instrumental analysis. Samples were stored at −20°C until analysis using high performance liquid chromatography analysis (HPLC, Shimadzu, Japan) coupled with Q-trap 6500+ mass spectrometer (MS/MS, AB Sciex, Framingham, MA).

The chromatography separation was done using the column Kinetex 1.7 μm Biphenyl column (100 Å 50x 2.1mm, Phenomenex, Torrance, CA) at 40°C. The mobile phase A consisted of 95% water: 5% acetonitrile: 0.005% formic acid, while mobile phase B contained 5% water: 95% acetonitrile: 0.005% formic acid. The gradient program was: 0–10min: 5%−100% mobile phase B; 10–12: hold at 100% mobile phase B; 12–12.9: 100% – 5% mobile phase B. The system was equilibrated for 3 min before each run. The flowrate was 0.4ml/min and the injection volume was 5μl. Electrospray ionization was used in negative mode with the ion spray voltage 4500V, curtain gas set at 40 psi, nebulizer gas

at 65 psi, turbo gas at 65 psi, source temperature at 650°C, and collision gas at 9 psi. Data processing was carried out using Multiquant software version 3.0.3.

Method detection limits were 18.33 pg/ml for 1-NAP, 12.75 pg/ml for 2-NAP, 7.64 pg/ml for 2-FLU, 20.29 pg/ml for 1-PHEN, 10.74 pg/ml for 2&3-PHEN, 11.75 pg/ml for 4-PHEN, and 18.41 pg/ml for 1-PYR. Instrument performance was checked for each run by running several mid-range concentration standards, and relative standard deviation was less than 15%. Every three samples, a methanol blank was injected to confirm that there was no carry-over between analyses. Instrumental intra-day precision was determined by running duplicate samples with an average of coefficient variation within the range 3–10% for 45 duplicates. Sixty homogenous pooled urine and synthetic urine samples were processed and measured along with actual urine samples in different batches. The averaged coefficient of variation (CV) of detected PAH metabolites ranged from 7–21%.

2.4. Outdoor, indoor, and dietary sources of PAH exposure assessed by questionnaire

We examined associations of PAH metabolite concentrations with season of urine sample collection and region of residence at sample collection, and with several sources of PAH exposure assessed by questionnaire. Adapting a questionnaire developed for the Long Island Breast Cancer Study Project (White et al., 2014), participating mothers completed the California PAH Study questionnaire that assessed the girls' lifetime residential history and asked for each residence about the following sources of PAH exposure: (i) outdoor sources, including neighborhood traffic (light, moderate, heavy), and type of neighborhood (residential, commercial, industrial); (ii) indoor sources, including fuel used for heating (electric, gas, coal, oil, firewood, synthetic fire logs), fuel used for indoor cooking (electric, gas, firewood, synthetic logs), use of fireplace (wood, synthetic logs, gas), and use of candles or incense in the home; and (iii) dietary sources, including frequency of cooking using a grill or barbecue. We examined the residential sources of PAH exposures that pertained to the girls' residence at the time of urine collection.

The California PAH Study questionnaire also asked mothers and girls aged ≥10 years about the girls' frequency of consumption of grilled or smoked meats, poultry or fish in the last 48 hours. Girls aged ≥10 years were asked about cigarette smoking and exposure to cigarette smoke at home or away from home in the last 48 hours. These analyses were limited to girls who provided a urine sample within 2 days of completing the questionnaire.

Two additional sources of PAH exposure were assessed in the 6-months and 12-months follow-up questionnaires in the LEGACY Girls Study. Indoor smoke exposure was based on a question about the number of household smokers. Neighborhood walkability due to street traffic was based on a question that asked about the level of agreement (strongly disagree, somewhat disagree, somewhat agree, strong agree) with the following statement "There is so much traffic on the streets that it makes it difficult or unpleasant to walk in my daughter's neighborhood". We used information on these two sources of PAH exposure for girls who lived at the same residence at first urine sample collection and at the 6-months or 12-months follow-up, respectively.

2.5. Statistical analysis

To account for urine dilution, metabolite concentrations were corrected for SG using the formula by Hauser et al. (2004): $P_c = P \times [SG_p\text{-}1)/(SG\text{-}1)]$, where P is the measured metabolite concentration in ng/L, SG is the specific gravity of the urine sample, and SG_p (1.022) is the median SG of the samples in the California PAH Study. Concentrations below the limit of detection (LOD) were assigned a value of LOD divided by the square root of 2. The LOD for each PAH metabolite is shown in Table 1. PAH metabolite concentrations were natural-log (ln) transformed for all analyses. Geometric means were compared across categories of participant characteristics using one-way analysis of variance (ANOVA). Correlation between pairs of PAH metabolites was assessed using Spearman correlation coefficients (SCC), calculated separately for first (N=359) and last (N=349) samples.

To assess consistency of repeated metabolite measurements on the same individual, we calculated SCC between measurements in first and last samples, adjusting for time (months) between samples. Additionally, we calculated intra-class correlation coefficients (ICC) in a one-way random-effects ANOVA model (Hertzmark et al., 2010) where the ICC represents the proportion of total variance due to the variance between individuals. In epidemiologic analyses exposures are often categorized into quantiles such as tertiles. We therefore also assessed how well the tertile classification of metabolite concentrations in a single sample (first or last sample) agreed with the tertile classification based on the average concentration of two samples. We calculated weighted Cohen's kappa statistics to assess agreement between the two tertile classifications. We repeated this analysis for 72 girls with PAH metabolites measured in three samples.

We assessed variation in PAH metabolites across categories of participant characteristics, including body mass index (BMI). The two weight and height measurements at first urine collection were averaged, and BMI was calculated as weight (kg) divided by squared height (m). BMI-for-age percentiles were calculated using the 2000 growth charts from the U.S. Centers for Disease Control and Prevention (CDC, 2000). We used multivariable linear regression, with a generalized estimating equations (GEE) approach to account for correlations among girls from the same family. Differences in means across categories are presented as ratios of mean metabolite concentrations (e^{β}) for girls with the source of PAH exposure of interest vs. the referent group. Using similar models, we assessed variation in metabolites across sources of PAH exposure. For some of the metabolites, mean concentrations varied significantly by age at urine collection, race/ethnicity, mother's education, and BMI percentile at urine collection (Table 1). All regression models were adjusted for these variables and ln(SG).

Since 1-NAP is a metabolite of both naphthalene and the insecticide carbaryl, but 2-NAP is a metabolite of naphthalene only, the ratio of 1-NAP to 2-NAP has been proposed as an indicator of carbaryl exposure (i.e., ratio >2) (Meeker at al., 2007). We assessed variation in the 1-NAP to 2-NAP ratio by participant and sample collection characteristics and sources of PAH exposure assessed by questionnaire, and in sensitivity analyses, we excluded girls with a 1-NAP to 2-NAP ratio >2.

3. Results

3.1. Participant characteristics and sources of PAH exposure

Of 359 girls with urinary PAH metabolite measurements (Table 1), most girls were non-Hispanic White (48%) or Hispanic (29%), 53% had a family history of breast cancer, 59% of mothers had a college or higher degree, 52% were from families with an annual income ≥100,000, and 24% had a BMI-for-age percentile of ≥85 (overweight or obese). Most urine samples were collected in the Fall (43%) or Winter (26%). Information on indoor and outdoor PAH exposure sources collected in the residential history was available for a subset of girls (N=210). Most girls lived in residential neighborhoods (91%), and nearly half lived in neighborhood with moderate or heavy traffic (46%), or with traffic that rendered walking difficult or unpleasant (43%). Indoor sources of PAH exposure included residential heating by gas (66%) and at least monthly use of candles or incense (28%). Few girls lived in homes with use of a fireplace at least 6 times per year (6%) or with smokers (7%), and 16% of girls reported exposure to cigarette smoke at home or away from home within 48 hours of urine sample collection. Regarding dietary sources of PAH exposure, 20% of girls lived in homes with at least monthly cooking using a grill or barbecue, and nearly half of the girls consumed grilled meat or fish (46%) or smoked meat or fish (37%) within 48 hours of urine sample collection.

3.2. Detection rate of urinary metabolites and correlations between metabolites

PAH metabolites were detected in a large proportion of first urine samples: ≥98% for 2-NAP, 1-PHEN, 2&3-PHEN, and 1-PYR; 82% for 1-NAP and 2&3-FLU; and 70% for 4-PHEN (Table 2). Concentrations varied widely, and were highest for 2-NAP and 1-NAP. Values for SG-corrected and SG-uncorrected concentrations were similar. The PAH detection rate was similarly high in the 349 last samples: ≥95% for 2-NAP, 2&3-FLU, 2&3-PHEN, 1-PHEN, and 1-PYR; 87% for 1-NAP; and 72% for 4-PHEN (data not shown in Table 2). Concentrations were highest for 2-NAP and 1-NAP.

All PAH metabolites were correlated with each other ($p < 0.001$), except for 1-NAP and 2-NAP (Supplemental Table 1). Correlations were strong between 1-PHEN and 2&3-PHEN (SCC 0.82) and 1-PHEN and 4-PHEN (SCC 0.70), and moderate between fluorene, phenanthrene and pyrene metabolites (SCC 0.43–0.62). 1-NAP and 2-NAP were weakly correlated with the other metabolites (SCC 0.18–0.36), except for 1-NAP and 4-PHEN (SCC 0.43). When we excluded 91 (25%) girls with a 1-NAP to 2-NAP ratio >2 (suggestive of carbaryl exposure), a weak correlation emerged between 1-NAP and 2-NAP (SCC 0.29, $p<0.0001$), whereas correlations between 1-NAP and the other metabolites did not change appreciably (data not shown). In 349 last urine samples, correlations between PAH metabolites were comparable to those seen in first samples (data not shown).

Among 349 girls with PAH metabolite measurement in two samples, SCC adjusted for time between the two samples was moderate for 2-NAP (0.49), and ranged from 0.15 to 0.35 for all other metabolites, and ICC ranged from 0.08 to 0.27 (Supplemental Table 2). When we classified metabolite concentrations into exposure tertiles based on single samples (first or last samples) vs. the average of the two samples, agreement was moderate to substantial,

with weighted kappa statistics ranging from 0.52–0.65 for the seven metabolites (Table 3). Agreement was similar for samples collected 6–54 months (kappa 0.49–0.63) vs. 55–72 months (kappa 0.49–0.66) apart. Agreement was also similar for younger (kappa 0.50–0.66) and older (kappa 0.48–0.62) girls. Among 72 girls with metabolite measurement in 3 samples, agreement was moderate when comparing exposure tertiles from the first samples vs. the average of three samples (kappa 0.47–0.57).

3.3. Urinary PAH metabolites by participant characteristics and sources of PAH exposure

In first urine samples, mean metabolite concentrations varied significantly across categories of participant characteristics and sources of PAH exposure for select metabolites (Supplemental Table 3), such as age (2-NAP, 1-PHEN), race/ethnicity (1-NAP, 2-NAP, 1-PHEN, 2&3-PHEN), mother's education (2-NAP), family income (2-NAP), and BMI percentile (2-NAP, 2&3-FLU). 1-NAP to 2-NAP ratio varied by race/ethnicity (higher ratio in non-Hispanic White girls), mother's education and family income (higher ratios for higher education and higher income), and BMI percentile (higher ratio for lower BMI percentile) (data not shown). Mean metabolite concentrations varied by season of sample collection (2-NAP, 1-PHEN, 2&3-PHEN, 4-PHEN, 1-PYR), were higher in neighborhoods with moderate or heavy traffic (2&3-FLU), in homes heated with gas (1-PHEN, 2&3-PHEN) or with use of candles or incense (2-NAP), and with consumption of smoked meat or fish (2-NAP).

In multivariable-adjusted regression models (Table 4), metabolite concentrations tended to be higher in girls aged 10–13 years than in younger girls, with the exception of 1-NAP. Compared to non-Hispanic White girls, 1-NAP was higher among African-American girls and borderline higher among Asian-American girls, 2-NAP was higher among Hispanic girls, and 1-PHEN and 2&3 PHEN were lower among Hispanic and African-American girls. 2-NAP and 1-PYR varied by mother's education. 2-NAP was higher among girls whose mother had less than a college degree and 1-PYR tended to be higher among those whose mother had a college degree or less. Among girls with a BMI percentile ≥85, 2&3-FLU and 1-PHEN were higher, and 4-PHEN was borderline higher. When we restricted the analysis to 268 girls with a 1-NAP to 2-NAP ratio ≤2, 1-NAP metabolites were 2- to 3-fold higher among Asian-American and African-American girls compared to non-Hispanic White girls (data not shown).

3.4. Urinary PAH metabolites by sources of PAH exposure

Supplemental Table 4 shows variability in PAH exposures overall and by race/ethnicity. African-American and Hispanic girls were more likely to live in mixed residential/commercial/industrial neighborhoods, Hispanic girls and those of mixed race/ethnicity were more likely to live in neighborhoods with low walkability due to traffic and in homes with smokers, and African-American and non-Hispanic White girls were more likely to live in homes with frequent use of candles or incense.

Associations of urinary PAH metabolites with outdoor and indoor sources of PAH exposure are shown in Table 5. We found some variation in metabolite concentrations by season of sample collection. Compared to summer samples, 2-NAP was higher in fall samples

(e^{β}=1.68, 95% CI=1.07–2.66) and borderline higher in winter samples, whereas the other metabolites tended to be lower in fall samples (2&3-FLU, 1-PHEN, 4-PHEN, 1PYR, e^{β} ranging from 0.49–0.75), winter samples (1-PHEN, 2&3-PHEN, 4-PHEN, e^{β} ranging from 0.63–0.76), or spring samples (2&3-FLU, 1-PHEN, e^{β}=0.48 and 0.73, respectively). 2&3-PHEN (e^{β}=1.21, 95% CI=1.01–1.47) and 4-PHEN (e^{β}=1.26, 95% CI=1.00–1.58) were higher in girls who lived in Peninsula/San Francisco/North Bay counties compared to East Bay counties.

Living in neighborhoods with low walkability due to traffic was associated with higher concentrations of 2-NAP (e^{β}=1.45, 95% CI=1.00–2.09) and 2&3-FLU (e^{β}=1.57, 95% CI=0.93–2.67), and living in neighborhoods with moderate or heavy traffic was associated with higher 2&3-FLU (e^{β}=1.90, 95% CI=1.09–3.31). Living in homes heated with gas was associated with higher 1-PHEN (e^{β}=1.21, 95% CI=1.00–1.48) and 2&3-PHEN (e^{β}=1.25, 95% CI=1.02–1.52), whereas cooking with a gas vs. electric stove was associated with lower 2&3-FLU (e^{β}=0.51, 95% CI=0.31–0.84) and 1-PHEN (e^{β}=0.80, 95% CI=0.66–0.96) and borderline lower 2&3-PHEN and 1-PYR. Higher 2-NAP was associated with living in a home with use of incense or candles (3–11 times per year: e^{β}=1.65, 95% CI=1.12–2.42), although more frequent use was not associated with higher 2-NAP concentrations. Living in a home with smokers was not associated with any PAH metabolite, but girls with cigarette smoke exposure in the last 48 hrs had borderline higher 2-NAP (e^{β}=1.23, 95% CI=0.97–1.57) and higher 2&3-PHEN (e^{β}=1.48, 95% CI=1.05–2.10) concentrations. Restricting the analysis to girls with a 1-NAP to 2-NAP ratio ≤2, 1-NAP was not associated with any outdoor or indoor sources of PAH exposure (data not shown), except for living in South Bay counties (e^{β}=2.01, 95% CI=1.06–3.81).

Associations of urinary metabolites with dietary sources of PAH exposure are shown in Table 6. Living in a home with frequent use of a grill or barbecue was associated with higher 2-NAP (1–3 times/month: e^{β}=1.77, 95% CI=1.02–3.09; ≥1/week: e^{β}=1.93, 95% CI=0.99–3.74). 2-NAP was also higher in girls who consumed smoked meat or fish in the last 48 hrs (e^{β}=1.77, 95% CI=1.16–2.68). Consumption of grilled meat or fish in the last 48 hrs was not associated with 2-NAP or any other PAH metabolite. Restricting the analysis to girls with a 1-NAP to 2-NAP ratio ≤2 did not show any associations with 1-NAP (data not shown).

4. Discussion

Analyses of seven urinary PAH metabolites in girls aged 6–16 years from the San Francisco Bay Area confirm widespread PAH exposures. The seven metabolites were detected in a large proportion of urine samples, with a wide range of concentrations for each metabolite, and 2-NAP and 1-NAP having the highest concentrations. For select metabolites, concentrations varied by the girls' age at urine collection, race/ethnicity, and BMI percentile, and we found associations with outdoor (season of sample collection, neighborhood traffic), indoor (heating with gas, use of candles or incense, cigarette smoke exposure), and dietary (frequent use of grill, consumption of smoked meat or fish) sources of PAH exposure.

The high detection rate of urinary PAH metabolites in our study of girls aged 6–16 years is consistent with the detection rates in the California component of the Breast Cancer and

the Environment Research Program (BCERP) study conducted in the San Francisco Bay Area that measured ten urinary PAH metabolites in 431 girls aged 6–8 years (Dobraca et al., 2018). Detection rates were also high in a national sample of participants in the 2011–2014 National Health and Nutrition Examination Survey (NHANES) that measured nine urinary PAH metabolites in ~400 children aged 6–11 years and ~400 adolescents aged 12–19 years (CDC, 2021). Urinary metabolite concentrations in our study were generally comparable to those in BCERP (Dobraca et al., 2018) and NHANES (CDC, 2021), except for lower concentrations of 2-NAP in our study compared to NHANES, and higher concentrations of 1-PYR in our study than in BCERP and NHANES. Even when we restricted the analysis to girls aged 6–8 years (as in BCERP) or aged 6–11 years (as in NHANES), 1-PYR concentrations were higher in our study, with similar findings in last urine samples. In children around the world, mean PAH metabolite concentrations vary considerably between studies, as summarized by Fernandez et al. (2021), reflecting differences in PAH exposures.

PAH metabolites were correlated with each other, with the strongest correlations between the three phenanthrene metabolites and moderate correlations between the fluorene, phenanthrene and pyrene metabolites, suggesting similar sources of PAH exposure. Consistent with the BCERP study (Dobraca et al., 2018), correlations between 1-NAP and 2-NAP and their correlations with other metabolites were weak, suggesting different exposure sources for the naphthalene metabolites. 1-PYR, the most frequently used biomarker of PAH exposures (Jongeneelen et al., 2001), was only weakly correlated with naphthalene metabolites and moderately correlated with the fluorene and phenanthrene metabolites, emphasizing the importance of examining multiple PAH metabolites, not just 1-PYR, in order to capture multiple sources of PAH exposure through urinary biomarkers.

Because urinary PAH metabolites have short half-lives of less than 48 hours (Li et al., 2012), it is important to assess whether a single measurement of urinary metabolites reflects longer-term exposure. SCC and ICC between metabolites measured in first and last samples were moderate or weak in our study, similar to the findings in BCERP (Dobraca et al., 2018), but agreement was moderate or substantial when classifying exposure into tertiles based on concentrations in single samples vs. average concentrations measured in two or three samples collected over a period of up to 72 months. These findings suggest that in girls aged 6–16 years measurement in a single urine sample provides reliable ranking into exposure tertiles. BCERP also found that a single sample accurately ranked metabolite concentrations into exposure quartiles when compared to the average concentrations from three samples collected over a 48-months period (Dobraca et al., 2018). These findings are reassuring, as not all epidemiologic studies have the opportunity to collect repeated urine samples over time.

Compared to urine samples collected in the summer, we found lower concentrations in fall samples (2&3-FLU, 1-PHEN, 4-PHEN, 1-PYR) and winter samples (1-PHEN, 2&3-PHEN, 4-PHEN). These findings may be related to higher air pollution levels and higher ambient temperature in late spring and summer, or higher frequency of grilling in the summer. The 3- or 4-ringed PAHs (FLU, PHEN, and PYR) are semi-volatile, and the higher ambient temperature in the summer leads to the preferential partitioning to the gas phase than to the particle phases (Odabasi et al., 1999). On the other hand, compared to summer samples,

2-NAP concentrations were higher in fall samples and borderline higher in winter samples, possibly suggesting higher PAH levels in ambient air when homes are being heated (Liu et al., 2017). The BCERP study also found some seasonal variation in urinary metabolites (Dobraca et al., 2018). Unlike in our study, in BCERP 1-NAP concentrations were two- to three-fold higher in spring, fall, or winter samples compared to summer samples, and 2-NAP concentrations were higher in spring samples.

Our finding of higher metabolite concentrations among girls aged 10–13 years than those aged 6–9 years is consistent with NHANES (2003–2014), where adolescents had higher concentrations than children (Jain, 2020). Variation in metabolite concentrations by race/ethnicity in our study is also consistent with NHANES and BCERP (CDC, 2021; Dobraca et al., 2018; Jain, 2020), although for specific metabolites variation by race/ethnicity differed across studies. The higher 2-NAP concentration in Hispanic girls compared to non-Hispanic White girls in our study is consistent with NHANES (Jain, 2020) and BCERP (Dobraca et al., 2018). 2&3-FLU metabolites did not differ by race/ethnicity in our study, whereas in NHANES 3-FLU varied by race/ethnicity, but not 2-FLU (Jain, 2020). We found lower concentrations of 1-PHEN and 2&3-PHEN metabolites among Hispanic and African-American girls compared to non-Hispanic White girls, whereas in NHANES 3-PHEN concentrations were higher among non-Hispanic White and African-American children compared to Hispanic children. In BCERP, there were no differences by race/ethnicity for the sum of the four phenanthrene metabolites Dobraca et al., 2018). Our data suggest differences in sources of PAH exposure by race/ethnicity that likely contribute to racial/ethnic differences in metabolite concentrations.

In NHANES (2003–2014), exposure to tobacco smoke at home was associated with urinary PAH metabolites in children aged 6–11 years, including 2-FLU, 9-FLU, 1-PHEN, 2-PHEN, 3-PHEN, and 1-PYR, but not with 1-NAP and 2-NAP (Jain, 2020). Similarly, in a German biomonitoring study (2014–2017) of 497 children aged 3–17 years, exposure to household smokers was associated with 1-NAP, 2-NAP, 2-FLU, and 1-PYR, but not with any of the phenanthrene metabolites, and naphthalene and pyrene concentrations increased with increasing number of smokers (Murawski et al., 2020). In contrast, we found no association of PAH metabolites with living in a home with smokers, but only 19 (7.3%) girls lived in a home with smokers at the time of urine collection, compared to 39% of German children (Murawski et al., 2020). We found an association among girls who reported cigarette smoke exposure during the 48 hours prior to urine collection, with higher concentrations of 2&3-PHEN and 2-NAP (borderline). A study in adult smokers, however, has shown that fluorene and 2-NAP metabolites were more strongly associated with smoking than phenanthrene metabolites (St. Helen et al., 2012). In our study, tobacco smoke exposure was based on self-report and subject to misclassification. In BCERP, tobacco smoke exposure was assessed through urinary cotinine measurements. That study found consistent associations between urinary cotinine and PAH metabolite concentrations, with the strongest associations found for 1-NAP, 2-NAP, and fluorene metabolites (Dobraca et al., 2018). In our study, only one girl reported smoking, but not in the last 48 hours, precluding analysis of active smoking.

Other sources of indoor PAH exposure include wood-burning fireplaces (Cirillo et al., 2006; Gustafson et al., 2008), and burning of incense or candles (Masih et al., 2010; Tang et al.,

2019). We found an association between 2-NAP and use of candles or incense, although there was no dose response gradient with frequency of use.

Findings on the association between measures of traffic-related PAH exposure and PAH metabolites are not consistent. Using mother-reported neighborhood traffic and neighborhood walkability as a source of PAH exposure, we found that girls who lived in neighborhoods with low walkability due to traffic had higher concentrations of 2-NAP and borderline higher 2&3-FLU, 1-PHEN, and 2&3-PHEN, and girls who lived in neighborhoods with moderate or heavy traffic had higher 2&3-FLU metabolites. In the German biomonitoring study, PAH metabolites tended to be higher with increasing traffic intensity (Murawski et al., 2020), whereas in the BCERP cohort a measure of distance-weighted traffic density around the girls' residence was not associated with urinary PAH metabolites (Dobraca et al., 2018). Similarly, in NHANES (2001–2004), distance to major roads was not associated with urinary PAH metabolites in children aged 8–15 years (Kim et al., 2021). Use of improved measures of PAH exposure sources such as air pollution sampling may generate more consistent associations with PAH exposure from vehicle exhaust.

For dietary sources of PAH exposure, we found higher 2-NAP PAH metabolites in girls who lived in homes where a grill was used at least once a month or consumed smoked meat or fish within 48 hours of urine collection. Whereas we found no association with consumption of grilled meat or fish, BCERP found that consumption of grilled food within 2 days of urine collection was associated with higher 1-NAP, fluorene, and phenanthrene metabolites and borderline higher 2-NAP and 1-PYR metabolites (Dobraca et al., 2018). Similarly in the German biomonitoring study, concentrations of 1-NAP, 2-FLU, and 1-PYR metabolites were higher among children who consumed barbecued food within 48 hours of urine collection (Murawski et al., 2020). The null association in our study was based on a much smaller sample size, with data on recent consumption of grilled meat or fish available for 142 girls.

Our study has several strengths. The urine collection rate at baseline was very high at 99%, and at least two urine samples were available for 96% of enrolled girls. These high collection rates demonstrate the feasibility of urine collection among children using a self-collection kit. Unlike other studies that used spot urine sampling (CDC, 2021; Dobraca et al., 2018), we collected a first-void morning urine sample which standardized the sample collection time and reduced the possibility of urinary dilution. As expected, PAH metabolite concentrations with or without correction for specific gravity were very similar. It is reassuring that Li et al. (2010) found a high correlation between first-void and 24-hour void samples. The study had a relatively long follow-up, with up to 72 months between first and last urine sample collection and a median time of 54 months. Even though PAH metabolites have short half-lives, we showed good agreement between classification of metabolite concentrations into tertiles based on single samples vs. the average of two or three samples collected over time. The study enrolled girls across a wide range of ages (6–16 years) which allowed us to evaluate whether agreement in tertile classification from single vs. average of two samples differed between younger and older girls. We found similar agreement for the two age groups. Our study sample was diverse, and we showed some differences in metabolite concentrations and sources of PAH exposure by race/ethnicity.

However, analyses by race/ethnicity were limited by small sample sizes, particularly for African-American girls, and larger studies that include diverse populations are warranted. Information on PAH exposure sources was based on self-report, and is therefore subject to exposure misclassification. Nevertheless, we found associations between metabolites and several sources of PAH exposure assessed by questionnaire that are generally consistent with those from other studies. However, our finding of an association between 2&3-PHEN and exposure to cigarette smoke exposure within 48 hours of urine collection is not consistent with other studies that measured urinary cotinine which is a superior measure than self-report (St. Helen et al., 2012; Dobraca et al., 2018). Furthermore, the small sample size of only 126 girls may also have contributed to the inconsistent results. Other important data sources on PAH exposure will need to be considered in future studies, including air pollution data. This may be particularly important in California, given increased wildfires in recent years that have adversely affected air quality.

5. Conclusions

The findings from the present study and other studies in children (Murawski et al. 2020; Dobraca et al., 2018; Jain, 2020) confirm that most children have detectable levels of urinary PAH metabolites and that these metabolites are associated with sources of PAH exposure that are potentially modifiable in the home environment. They could be targeted for reduction in PAH exposures, such as reducing exposure to cigarette smoke and consumption of charred meat grilled at high temperature, and avoiding frequent burning of incense or candles. At the community level, lowering air pollution from vehicle and industrial emissions are critical to reduce PAH exposures. Given that many PAHs are classified as probable carcinogens, are suspected endocrine-disrupting chemicals, and have been associated with a number of adverse health effects (Kim et al., 2013), continued efforts to reduce PAH exposures are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BCERP	Breast Cancer and the Environment Research Program
BMI	body mass index
CI	confidence interval
FLU	fluorine

GEE	generalized estimating equations
ICC	intra-class correlation coefficients
LEGACY	Lessons in Epidemiology and Genetics and Adult Cancer from Youth
LOD	limit of detection
NAP	naphthalene
NHANES	National Health and Nutrition Examination Survey
PAH	polycyclic aromatic hydrocarbons
PHEN	phenanthrene
PYR	pyrene
SCC	Spearman correlation coefficient
SG	specific gravity
U.S.	United States

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Table 1.

Characteristics and sources of PAH exposure of girls with urinary PAH metabolite measurement, California PAH Study, 2011–2020

	N	%
Sociodemographic and other characteristics		
Age at urine collection (years)		
6–9	153	43%
10–13	181	50%
14–16	25	7%
Race/ethnicity		
Non-Hispanic white	173	48%
Hispanic	104	29%
Asian American [a]	47	13%
African American	22	6%
Mixed race	13	4%
Family history of breast cancer [b]		
No	164	46%
Yes	192	53%
Unknown	3	1%
Mother's education		
Some college or less	122	34%
College degree	90	25%
Graduate degree	122	34%
Unknown	25	7%
Family income ($)		
<50,000	62	17%
50,000 – 99,999	65	18%
≥100,000	187	52%
Unknown	45	13%
BMI-for-age percentile at urine collection		
<50	163	45%
50 – <85	111	31%

	N	%
≥85	85	24%
Outdoor sources of PAH exposure		
Region of residence [c]		
East Bay	164	46%
South Bay	126	35%
Peninsula, San Francisco, North Bay	69	19%
Season of urine sample collection [d]		
Summer	72	20%
Fall	154	43%
Winter	94	26%
Spring	39	11%
Type of neighborhood [e]		
Residential	192	91%
Other [f]	18	9%
Traffic in neighborhood [e]		
Light	112	54%
Moderate/Heavy	97	46%
Neighborhood walkability due to street traffic [g]		
High	159	57%
Medium	77	28%
Low	43	15%
Indoor sources of PAH exposure		
Fuel for residential heating [e,h]		
Electric	65	33%
Gas	133	67%
Fuel for indoor cooking [e]		
Electric	76	36%
Gas	133	64%
Use of wood or synthetic logs in fireplace [e]		

	N	%
Never	132	71%
1–2 times per year	19	10%
3–5 times/year	21	11%
≥6 times/year	13	7%
Use of candles or incense in home [e]		
Never or 1–2 times/year	108	52%
3–11 times/year	42	20%
≥1 times/month	58	28%
Smokers in household [i]		
No	243	93%
Yes	19	7%
Cigarette smoke exposure within 48 hours of urine collection [j]		
No	106	84%
Yes	20	16%
Dietary sources of PAH exposure		
Frequency of cooking using grill or barbecue [e]		
Never or 1–2 times/year	72	53%
3–11 times/year	60	44%
1–3 times/month	50	36%
≥1 per week	27	20%
Consumption of grilled meat or fish within 48 hours of urine collection [k]		
No	77	54%
Yes	65	46%
Consumption of smoked meat or fish within 48 hours of urine collection [k]		
No	60	63%
Yes	35	37%

Abbreviations: PAH, polycyclic aromatic hydrocarbons.

[a] Includes 3 Pacific Islander girls.

[b] In first- or second-degree relatives.

[c] Peninsula/San Francisco/North Bay: San Mateo (N=32), San Francisco (N=27), and Marin (N=8) counties; South Bay: Santa Clara (N=121) and Santa Cruz (N=5) counties; East Bay: Alameda (N=73), Contra Costa (N=86), Stanislaus (N=4), and Solano (N=1) counties.

[d] Spring: March-May; Summer: June-August; Fall: September-November; Winter: December-February.

[e] PAH metabolites were measured in urine samples collected at baseline of the LEGACY Girls Study and were linked for 210 girls to sources of PAH exposure in the residence at baseline (reported by mothers in the residential history collected in the California PAH Study).

[f] Commercial or industrial, or a combination of residential, commercial and industrial.

[g] PAH metabolites were measured in urine samples collected at baseline of the LEGACY Girls Study and linked to information on neighborhood walkability (reported by mothers at the 6-months follow-up) for 279 girls who lived at same address at baseline and at the 6-months follow-up. Neighborhood walkability due to street traffic was coded as high, medium, or low based on level of agreement (strongly disagree, somewhat disagree, strongly or somewhat agree) with the following statement: “There is so much traffic on the streets that it makes it difficult or unpleasant to walk in my daughter’s neighborhood”.

[h] No participant reported using coal, oil, or wood for heating.

[i] PAH metabolites were measured in urine samples collected at baseline of the LEGACY Girls Study and linked to information on number of household smokers (reported by mothers at the 12-months follow-up) for 262 girls who lived at same address at baseline and at the 12-months follow-up.

[j] Cigarette smoke exposure at home or away from home, reported by girls aged ≥10 years who participated in the California PAH Study. PAH metabolites were measured in urine samples collected at enrollment in the California PAH Study enrollment, and the analysis was restricted to 126 samples collected within 48 hours of questionnaire completion.

[k] The analysis was based on reports by girls aged ≥10 years who participated in the California PAH Study, supplemented with mother reports if the girls did not answer the questions on dietary sources of PAH exposure. PAH metabolites were measured in urine samples collected at enrollment in the California PAH Study, and the analysis was restricted to 155 samples collected within 48 hours of questionnaire completion.

Table 2.

Geometric mean (GM) concentrations (ng/L) of SG-corrected PAH metabolites in first urine samples (N=359), California PAH Study, 2011–2020

PAH metabolite	N	1-hydroxy naphthalene	2-hydroxy naphthalene	2- and 3-hydroxy fluorene	1-hydroxy phenanthrene	2- and 3-hydroxy phenanthrene	4-hydroxy phenanthrene	1-hydroxy pyrene
LOD (ng/L)		18.33	12.75	7.64	20.29	10.74	11.75	18.41
Samples >LOD (N)		296	352	293	353	356	251	356
Samples >LOD (%)		82.5	98.1	81.6	98.3	99.2	69.9	99.2
Range, SG-corrected (min, max)		638–723,159	343–106,870	80–23,778	24–3,888	33–7,340	10–603	77–36,989
GM, SG-corrected (95% CI)	359	1,324 (1,041–1,684)	2,948 (2,594–3,351)	170 (141–204)	133 (123–144)	113 (105–122)	21 (19–23)	346 (319–375)
GM, not SG-corrected (95% CI)	359	1,308 (1,028–1,664)	2,794 (2,443–3,196)	171 (142–205)	130 (119–141)	109 (100–119)	21 (20–23)	327 (299–358)

Abbreviations: CI, confidence interval; GM, geometric mean; LOD, level of detection; PAH, polycyclic aromatic hydrocarbons; SG, specific gravity.

Table 3.

Agreement of tertile classifications of PAH metabolite concentrations [a] based on single samples vs. average concentration of 2 or 3 samples, California PAH Study, 20112020

		1-hydroxy naphthalene			2-hydroxy naphthalene			2- and 3-hydroxy fluorene			1-hydroxy phenanthrene			2- and 3-hydroxy phenanthrene			4-hydroxy phenanthrene			1-hydroxy pyrene		
		Tertile classification based on the average concentration of first and last samples from 349 girls [b, c]																				
		Low	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
Tertile classification of single samples (first and last; total 698 samples) [d]	Low	157	66	9	184	49	7	165	58	6	167	58	8	172	54	6	126	101	9	184	41	7
	Medium	48	122	65	41	131	50	47	131	61	59	117	55	46	75	36	30	155	46	91	112	30
	High	29	42	160	7	52	177	18	47	165	10	47	177	20	97	192	0	88	143	13	91	129
Weighted Cohen's Kappa [e] and 95% CI		0.52 (0.47 – 0.57)			0.65 (0.60 – 0.69)			0.58 (0.53 – 0.63)			0.59 (0.54 – 0.64)			0.56 (0.51 – 0.61)			0.52 (0.47 – 0.56)			0.52 (0.48 – 0.57)		
Weighted Cohen's Kappa [e] and 95% CI for 173 girls with 6–54 months between first and last sample		0.55 (0.48 – 0.62)			0.63 (0.57 – 0.70)			0.57 (0.50 – 0.64)			0.62 (0.55 – 0.68)			0.52 (0.46 – 0.59)			0.50 (0.43 – 0.56)			0.49 (0.42 – 0.56)		
Weighted Cohen's Kappa [e] and 95% CI for 176 girls with 55–72 months between first and last sample		0.49 (0.41 – 0.56)			0.66 (0.60 – 0.72)			0.58 (0.51 – 0.65)			0.57 (0.50 – 0.63)			0.59 (0.53 – 0.65)			0.53 (0.46 – 0.60)			0.54 (0.48 – 0.61)		
Weighted Cohen's Kappa and 95% CI for 148 girls aged 6–9 years at first sample collection		0.57 (0.49 – 0.64)			0.66 (0.60 – 0.73)			0.60 (0.53 – 0.68)			0.58 (0.51 – 0.65)			0.59 (0.52 – 0.66)			0.50 (0.42 – 0.57)			0.58 (0.51 – 0.65)		
Weighted Cohen's Kappa [e] and 95% CI for 201 girls aged 10–16 years at first sample collection		0.49 (0.42 – 0.56)			0.62 (0.56 – 0.68)			0.55 (0.49 – 0.62)			0.59 (0.53 – 0.65)			0.53 (0.47 – 0.60)			0.52 (0.46 – 0.59)			0.48 (0.41 – 0.55)		
		Tertile classification based on the average concentration of 3 samples from 72 girls [f, g]																				
		Low	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
Tertile classification of single samples (first, middle, and last; total 216 samples) [h]	Low	46	20	4	49	20	3	45	22	4	4	24	3	47	23	2	45	19	7	43	21	5
	Medium	19	33	23	17	37	15	23	34	18	18	32	20	19	29	20	23	31	15	18	37	19
	High	7	16	48	3	18	54	4	13	53	53	16	52	3	20	53	4	19	53	8	17	48
Weighted Cohen's Kappa e and 95% CI		0.48 (0.39 – 0.57)			0.57 (0.49 – 0.66)			0.52 (0.43 – 0.61)			0.49 (0.40 – 0.58)			0.52 (0.44 – 0.61)			0.49 (0.40 – 0.59)			0.47 (0.37 – 0.56)		

Table 2 is based on 349 girls with PAH metabolites measured in two samples (first and last sample) and 72 girls with PAH metabolites measured in three samples (first, middle, and last sample). The upper panel shows the agreement between two tertile classifications of concentrations for each of the seven PAH metabolites. Agreement was assessed between the tertile classification of concentrations in single samples (first or last samples) and the tertile classification of the average concentration of two samples. Agreement between the two tertile classifications was moderate to substantial (weighted kappa statistics 0.52–0.65). The lower panel of Table 2 shows the agreement between the tertile classification of concentrations in single samples (first, middle, or last samples) and the tertile classification of the average concentration of three samples. Agreement between the two tertile classifications was moderate (weighted kappa statistics 0.47–0.57).

[a] SG-corrected urinary PAH metabolite concentrations.

[b] This upper panel includes 349 girls with PAH metabolites measured in first and last samples (total 698 samples). For each PAH metabolite, the 3x3 cross tabulation shows tertile counts.

[c] For the column counts, the tertile cutpoints were based on the distribution of the average concentration of the first and last sample for each girl.

[d] For the row counts, first samples were classified as low, medium, or high according to the tertile distribution of concentrations of first samples; last samples were classified as low, medium or high according to the tertile distribution of concentrations of last samples. The counts sum to 698 samples that were classified as low, medium or high.

[e] Kappa values range from 0 to 1, with 0 indicating poor agreement and 1 indicating perfect agreement. Kappa values from 0–0.20 indicate slight agreement, 0.21–0.40 indicate fair agreement, 0.41–0.60 indicate moderate agreement, 0.61–0.80 indicate substantial agreement, and 0.81–1.0 indicate almost perfect agreement (Landis et al., 1977).

[f] This lower panel includes 72 girls with PAH metabolites measured in first, middle, and last samples (total 216 samples). For each PAH metabolite, the 3x3 cross tabulation shows tertile counts.

[g] For the column counts, the tertile cutpoints were based on the distribution of the average concentration of the first, middle, and last sample for each girl.

[h] For the rows counts, the first samples were classified as low, medium, or high according to the tertile distribution of concentrations of first samples; middle samples were classified as low, medium or high according to the tertile distribution of concentrations of middle samples; and last samples were classified as low, medium or high according to the tertile distribution of concentrations of last samples. The counts sum to 216 samples that were classified as low, medium or high.

Table 4.

Ratio of SG-corrected mean PAH metabolite concentrations (e^{β}) [a] in first urine samples (N=359), by participant characteristics, California PAH Study, 2011–2020

Characteristic	N	1-hydroxy naphthalene e^{β} (95% CI)	2-hydroxy naphthalene e^{β} (95% CI)	2- and 3-hydroxy fluorene e^{β} (95% CI)	1-hydroxy phenanthrene e^{β} (95% CI)	2- and 3-hydroxy phenanthrene e^{β} (95% CI)	4-hydroxy phenanthrene e^{β} (95% CI)	1-hydroxy pyrene e^{β} (95% CI)
Age at first urine collection (years)								
6–9	153	1.0	1.0	1.0	1.0	1.0	1.0	1.0
10–13	181	1.02 (0.62–1.68)	1.35 (1.06–1.73)	1.41 (0.96–2.06)	1.23 (1.07–1.42)	1.19 (1.03–1.37)	1.16 (0.97–1.38)	1.13 (0.97–1.33)
14–16	25	1.31 (0.39–4.39)	1.37 (0.94–2.00)	1.65 (1.01–2.71)	1.07 (0.82–1.41)	1.04 (0.81–1.34)	0.96 (0.69–1.34)	1.09 (0.77–1.54)
Race/ethnicity								
Non-Hispanic White	173	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Hispanic	104	0.81 (0.41–1.60)	1.52 (1.06–2.18)	0.79 (0.51–1.22)	0.70 (0.58–0.86)	0.68 (0.57–0.82)	0.87 (0.71–1.08)	0.99 (0.81–1.21)
Asian American [b]	47	1.85 (0.95–3.63)	0.93 (0.62–1.40)	0.94 (0.47–1.89)	1.06 (0.82–1.38)	1.08 (0.80–1.45)	1.22 (0.90–1.66)	1.07 (0.79–1.46)
African American	22	2.95 (1.13–7.71)	1.24 (0.85–1.82)	0.77 (0.39–1.53)	0.61 (0.45–0.84)	0.74 (0.55–0.98)	0.99 (0.72–1.36)	1.20 (0.85–1.70)
Mixed race/ethnicity	13	1.36 (0.52–3.55)	1.28 (0.82–1.97)	0.96 (0.30–3.09)	0.82 (0.47–1.44)	0.92 (0.53–1.59)	1.02 (0.61–1.71)	1.11 (0.63–1.95)
Mother's education								
Graduate degree	122	1.0	1.0	1.0	1.0	1.0	1.0	1.0
College degree	90	1.26 (0.64–2.48)	1.14 (0.76–1.70)	0.92 (0.56–1.52)	1.17 (0.95–1.45)	1.24 (0.99–1.55)	1.25 (0.97–1.61)	1.27 (1.03–1.56)
Some college or less	122	0.89 (0.47–1.72)	1.50 (1.03–2.17)	1.06 (0.65–1.74)	1.10 (0.89–1.36)	1.10 (0.90–1.34)	1.08 (0.86–1.35)	1.12 (0.90–1.40)
Unknown	25	0.71 (0.21–2.39)	1.37 (0.84–2.22)	0.94 (0.45–2.00)	1.01 (0.73–1.41)	0.92 (0.64–1.32)	1.18 (0.85–1.64)	1.52 (1.04–2.23)
BMI-for-age percentile at urine collection								
<50	163	1.0	1.0	1.0	1.0	1.0	1.0	1.0
50 – <85	111	1.15 (0.66–2.02)	1.24 (0.94–1.65)	1.19 (0.77–1.83)	1.01 (0.83–1.21)	1.02 (0.84–1.23)	0.99 (0.81–1.22)	0.90 (0.73–1.09)
≥85	85	1.26 (0.64–2.47)	1.30 (0.92–1.83)	2.01 (1.31–3.09)	1.29 (1.07–1.54)	1.06 (0.90–1.25)	1.23 (0.98–1.53)	0.97 (0.80–1.18)

Abbreviations: GEE, generalized estimating equations; PAH, polycyclic aromatic hydrocarbons; SG, specific gravity.

[a] From multivariable linear regression models with natural log transformed PAH metabolite concentration as the dependent variable, mutually adjusted for all variables shown in table and for ln(SG), and calculated using GEE to account for correlation among siblings from the same family.

[b] Includes 3 Pacific Islander girls.

Table 5.

Ratio of SG-corrected mean PAH metabolite concentrations (e^{β}) [a], by outdoor and indoor sources of PAH exposure, California PAH Study, 2011–2020

	N	1-hydroxy naphthalene e^{β} (95% CI)	2-hydroxy naphthalene e^{β} (95% CI)	2- and 3hydroxyfluorene e^{β} (95% CI)	1-hydroxy phenanthrene e^{β} (95% CI)	2- and 3-hydroxy phenanthrene e^{β} (95% CI)	4-hydroxy phenanthrene e^{β} (95% CI)	1-hydroxy pyrene e^{β} (95% CI)
Outdoor sources of PAH exposure								
Region of residence [b]								
East Bay	164	1.0	1.0	1.0	1.0	1.0	1.0	1.0
South Bay	126	1.64 (0.95–2.84)	1.25 (0.93–1.67)	1.01 (0.64–1.58)	1.00 (0.83–1.20)	1.02 (0.84–1.24)	1.15 (0.93–1.41)	1.12 (0.93–1.34)
Peninsula, San Francisco, North Bay	69	1.35 (0.69–2.65)	1.09 (0.73–1.62)	1.25 (0.77–2.04)	1.11 (0.91–1.36)	1.21 (1.01–1.47)	1.26 (1.00–1.58)	0.97 (0.77–1.22)
Season of sample collection [c]								
Summer	72	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Fall	154	0.48 (0.22–1.03)	1.68 (1.07–2.66)	0.49 (0.28–0.86)	0.75 (0.58–0.97)	0.86 (0.66–1.11)	0.73 (0.54–0.98)	0.70 (0.54–0.91)
Winter	94	0.87 (0.42–1.81)	1.48 (0.94–2.31)	0.88 (0.53–1.47)	0.63 (0.50–0.80)	0.76 (0.61–0.96)	0.65 (0.50–0.86)	0.81 (0.64–1.04)
Spring	39	1.08 (0.40–2.93)	1.42 (0.76–2.64)	0.48 (0.23–0.97)	0.73 (0.54–0.98)	0.87 (0.66–1.15)	0.79 (0.57–1.10)	0.77 (0.58–1.02)
Type of neighborhood [d]								
Residential	192	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Other [e]	18	0.77 (0.24–2.50)	1.29 (0.90–1.85)	1.18 (0.52–2.69)	1.00 (0.76–1.32)	1.13 (0.87–1.48)	1.32 (0.95–1.83)	1.10 (0.87–1.39)
Neighborhood traffic [d]								
Light	112	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Moderate/Heavy	97	0.78 (0.42–1.44)	0.99 (0.70–1.40)	1.90 (1.09–3.31)	1.09 (0.89–1.32)	1.08 (0.87–1.33)	1.02 (0.82–1.27)	1.11 (0.90–1.37)
Neighborhood walkability due to street traffic [f]								
High	159	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Medium	77	1.35 (0.69–2.68)	1.14 (0.82–1.58)	1.27 (0.78–2.08)	1.09 (0.89–1.33)	1.13 (0.93–1.37)	1.08 (0.86–1.36)	1.03 (0.85–1.26)

	N	1-hydroxy naphthalene e^{β} (95% CI)	2-hydroxy naphthalene e^{β} (95% CI)	2- and 3hydroxyfluorene e^{β} (95% CI)	1-hydroxy phenanthrene e^{β} (95% CI)	2- and 3-hydroxy phenanthrene e^{β} (95% CI)	4-hydroxy phenanthrene e^{β} (95% CI)	1-hydroxy pyrene e^{β} (95% CI)
Low	43	1.17 (0.55–2.49)	1.45 (1.00–2.09)	1.57 (0.93–2.67)	1.18 (0.97–1.42)	1.19 (0.96–1.47)	1.12 (0.87–1.44)	1.14 (0.90–1.43)
Indoor sources of PAH exposure								
Fuel for residential heating *d,g*								
Electric	65	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Gas	133	1.05 (0.51–2.13)	0.77 (0.54–1.08)	1.05 (0.62–1.79)	1.21 (1.00–1.48)	1.25 (1.02–1.52)	1.17 (0.93–1.47)	1.04 (0.86–1.26)
Fuel for indoor cooking *d*								
Electric	76	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Gas	133	0.93 (0.52–1.67)	0.76 (0.51–1.11)	0.51 (0.31–0.84)	0.80 (0.66–0.96)	0.86 (0.72–1.04)	0.86 (0.69–1.08)	0.82 (0.66–1.02)
Use of wood or synthetic logs in fireplace in the home *d,h*								
Never	132	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1–2 times/year	19	0.39 (0.10–1.44)	0.94 (0.56–1.56)	0.67 (0.29–1.54)	0.74 (0.54–1.00)	0.73 (0.52–1.04)	0.73 (0.52–1.01)	1.03 (0.77–1.39)
3–5 times/year	21	0.45 (0.16–1.30)	1.40 (0.88–2.23)	0.95 (0.42–2.13)	0.88 (0.65–1.20)	0.98 (0.70–1.38)	0.80 (0.54–1.18)	0.90 (0.65–1.24)
≥6 times/year	13	1.41 (0.43–4.71)	0.70 (0.23–2.12)	1.49 (0.60–3.68)	0.97 (0.61–1.54)	0.93 (0.59–1.46)	0.86 (0.53–1.39)	0.72 (0.39–1.32)
Use of candles or incense in the home *d*								
Never or 1–2 times/year	108	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3–11 times/year	42	1.23 (0.62–2.44)	1.65 (1.12–2.42)	0.97 (0.51–1.82)	1.04 (0.85–1.28)	1.00 (0.79–1.26)	1.03 (0.81–1.32)	0.90 (0.72–1.11)
≥1 times/month	58	0.73 (0.30–1.73)	1.13 (0.66–1.96)	0.82 (0.47–1.43)	0.92 (0.71–1.18)	0.90 (0.71–1.15)	1.02 (0.78–1.33)	0.98 (0.79–1.23)
Smokers in household *i*								
No	243	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	19	0.99 (0.36–2.72)	0.74 (0.45–1.20)	1.37 (0.58–3.25)	0.92 (0.64–1.32)	0.82 (0.56–1.22)	0.79 (0.54–1.17)	0.97 (0.67–1.41)

		1-hydroxy naphthalene	2-hydroxy naphthalene	2- and 3hydroxyfluorene	1-hydroxy phenanthrene	2- and 3-hydroxy phenanthrene	4-hydroxy phenanthrene	1-hydroxy pyrene
	N	e^{β} (95% CI)	e^{β} (95% CI)	e^{β} (95% CI)	e^{β} (95% CI)	e^{β} (95% CI)	e^{β} (95% CI)	e^{β} (95% CI)
Cigarette smoke exposure within 48 hours of urine collection [j]								
No	106	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	20	0.95 (0.22–4.13)	1.23 (0.97–1.57)	1.48 (0.64–3.44)	1.44 (0.92–2.26)	1.48 (1.05–2.10)	0.80 (0.60–1.07)	1.06 (0.80–1.40)

Abbreviations: GEE, generalized estimating equations; PAH, polycyclic aromatic hydrocarbons; SG, specific gravity.

[a] From multivariable linear regression models with natural log transformed PAH metabolite concentration as the dependent variable, adjusted for race/ethnicity (non-Hispanic White, Hispanic, Asian American/Pacific Islander, African American, mixed race/ethnicity), age (6–9, 10–13, ≥14 years), education (some college or less, Bachelor's degree, graduate degree, unknown), BMI-for-age percentiles (<50th, 50–84, ≥85th), and ln(SG), and calculated using GEE to account for correlation among siblings from the same family.

[b] Peninsula/San Francisco/North Bay: San Mateo (N=32), San Francisco (N=27), and Marin (N=8) counties; South Bay: Santa Clara (N=121) and Santa Cruz (N=5) counties; East Bay: Alameda (N=73), Contra Costa (N=86), Stanislaus (N=4), and Solano (N=1) counties.

[c] Spring: March-May; Summer: June-August; Fall: September-November; Winter: December-February.

[d] PAH metabolites measured in 210 urine samples collected at baseline of the LEGACY Girls Study that were linked to the exposures in the residence at baseline, taken from residential history reported by mothers who participated in the PAH Study. Only non-missing exposures are included in the analyses.

[e] Commercial or industrial, or a combination of residential and commercial or industrial.

[f] PAH metabolites measured in urine samples collected at baseline of the LEGACY Study from 279 girls who lived at same address at baseline and at 1st follow-up that collected information on neighborhood street traffic (reported by mother). Neighborhood walkability due to street traffic was coded as high, medium, or low based on level of agreement (strongly disagree, somewhat disagree, strongly or somewhat agree) with the following statement: "There is so much traffic on the streets that it makes it difficult or unpleasant to walk in my daughter's neighborhood"

[g] No participant reported using coal, oil, or wood for heating.

[h] Does not include unknown (N=1) or use of gas fireplace (N=24).

[i] PAH metabolites measured in urine samples collected at baseline of the LEGACY Study from 262 girls who lived at same address at baseline and at 2nd follow-up that collected information on number of household smokers (reported by mothers).

[j] At home or away from home. Reported by 126 girls who participated in the California PAH Study, PAH metabolites measured in urine samples collected at California PAH Study enrollment.

Table 6.

Ratio of SG-corrected mean PAH metabolite concentrations (e^{β}) [a], by dietary sources of PAH exposure, California PAH Study, 2011–2020

		1-hydroxy naphthalene	2-hydroxy naphthalene	2- and 3-hydroxy fluorene	1-hydroxy phenanthrene	2- and 3-hydroxy phenanthrene	4-hydroxy phenanthrene	1-hydroxy pyrene
	N	**e^{β} (95% CI)**	**e^{β} (95% CI)**	**e^{β} (95% CI)**	**e^{β} (95% CI)**	**e^{β} (95% CI)**	**e^{β} (95% CI)**	**e^{β} (95% CI)**
Frequency of cooking using a grill or barbecue [b,c]								
Never or 1–2 times/year	72	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3–11 times/year	60	1.07 (0.47–2.45)	1.33 (0.82–2.16)	1.17 (0.61–2.27)	1.10 (0.88–1.37)	1.10 (0.88–1.38)	1.11 (0.85–1.44)	1.00 (0.79–1.27)
1–3 times/month	50	0.71 (0.28–1.79)	1.77 (1.02–3.09)	1.27 (0.63–2.59)	0.94 (0.73–1.22)	0.97 (0.74–1.26)	1.03 (0.74–1.42)	0.97 (0.72–1.30)
≥1 per week	27	1.30 (0.46–3.63)	1.93 (0.99–3.74)	0.55 (0.20–1.47)	0.82 (0.56–1.20)	0.81 (0.55–1.20)	0.89 (0.62–1.27)	0.87 (0.65–1.18)
Consumption of grilled meat or fish within 48 hours of urine collection [d,e]								
No	77	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	65	1.59 (0.84–3.01)	0.86 (0.75–0.99)	0.86 (0.68–1.08)	0.98 (0.66–1.47)	0.92 (0.72–1.19)	0.79 (0.50–1.26)	0.85 (0.56–1.30)
Consumption of smoked meat or fish within 48 hours of urine collection [d,f]								
No	60	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	35	0.85 (0.41–1.76)	1.77 (1.16–2.68)	1.36 (0.99–1.86)	0.88 (0.68–1.14)	1.02 (0.77–1.35)	1.14 (0.86–1.50)	1.13 (0.89–1.42)

Abbreviations: PAH, polycyclic aromatic hydrocarbons; SG, specific gravity.

[a] From multivariable linear regression models with natural log transformed PAH metabolite concentration as the dependent variable, adjusted for race/ethnicity (non-Hispanic White, Hispanic, Asian American/Pacific Islander, African American, mixed race/ethnicity), age (6–9, 10–13, ≥14 years), education (some college or less, Bachelor's degree, graduate degree, unknown), BMI-for-age percentiles ($<50^{th}$, 50–84, $\geq 85^{th}$), and ln(SG), and calculated using general equation estimates (GEE) to account for correlation among siblings from the same family.

[b] PAH metabolites measured in 210 urine samples collected at baseline of the LEGACY Girls Study that were linked to the residential history reported by mothers who participated in the PAH Study. Only non-missing exposures are included in the analyses.

[c] Unknown N=1.

[d] Analysis based on PAH metabolites measured in 155 urine samples collected at California PAH Study enrollment. Exposures are based on daughter reports, supplemented with mother reports if daughter report was missing.

[e] Unknown N=13.

[f] Unknown N=60.