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Association Between Diet and Polycyclic Aromatic Hydrocarbon Biomarkers in Urine Among Pregnant Women in Los Angeles

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Association Between Diet and Polycyclic Aromatic Hydrocarbon Biomarkers in Urine Among Pregnant Women in Los Angeles

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Epidemiology

by

Kasey Elizabeth Yu

2024

ABSTRACT OF THE THESIS

Association Between Diet and Polycyclic Aromatic Hydrocarbon Biomarkers in Urine Among Pregnant Women in Los Angeles

by

Kasey Elizabeth Yu

Master of Science in Epidemiology

University of California, Los Angeles, 2024

Professor Beate R. Ritz, Chair

Introduction: Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous contaminants released by the combustion of fossil fuels, vegetation, and tobacco. Few studies have evaluated the relationship between diet and urinary PAH biomarkers among pregnant women.

Methods: We evaluated the associations between diet and PAH biomarkers in a prospective cohort study of pregnant women who gave birth at UCLA. Diet was evaluated with a past-month food frequency questionnaire and included information on portion sizes. Food category intake was calculated and used to produce three diet index scores: Healthy Eating Index (HEI) 2015,

Alternative Mediterranean Diet (aMED), and Alternate Healthy Eating Index for Pregnancy (AHEI-P). Urine samples were collected up to three times during pregnancy and analyzed for PAH biomarkers, including 2-hydroxyfluorene + 3-hydroxyfluorene (FLUO2FLUO3), 1-hydroxyphenanthrene (PHEN1), 2-hydroxyphenanthrene (PHEN2), 3-hydroxyphenanthrene (PHEN3), 4-hydroxyphenanthrene (PHEN4), 2-hydroxynaphthalene (NAP2), and 1-hydroxypyrene (PYR1). We employed multiple linear regression models to evaluate associations between diet and measured urinary PAHs and PAH summary measures.

Results: Higher compliance with healthier dietary patterns (HEI-2015, aMED, AHEI-P) was found to be associated with lower urinary PAHs. Furthermore, higher (≥median) total meat consumption was associated with an average increase and higher vegetable intake with an average decrease in several urinary PAH biomarkers (FLUO2FLUO3, NAP2, PHEN1, PHEN4, PYR1, sum of all phenanthrene biomarkers (ΣPHEN), and sum of all PAH biomarkers (ΣPAHs)).

Conclusion: Higher compliance with healthier dietary patterns lower PAH exposure, with higher meat consumption likely contributing to PAH exposures and higher vegetable consumption lowering PAH exposure.

The thesis of Kasey Elizabeth Yu is approved.

Liwei Chen

Elizabeth Rose Mayeda

Beate R. Ritz, Committee Chair

University of California, Los Angeles

2024

Dedication

To my family and friends for supporting me throughout all challenges.

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List of Abbreviations

AHEI-P: Alternate Healthy Eating Index for Pregnancy

aMED: Alternate Mediterranean Diet

DHQ II: Diet History Questionnaire II

FFQ: food frequency questionnaire

FLUO2FLUO3: 2-hydroxyfluorene + 3-hydroxyfluorene

HEI-2015: Healthy Eating Index 2015

NAP2: 2-hydroxynaphthalene

PAH: polycyclic aromatic hydrocarbons

ΣPAHs: sum of all PAH biomarkers

PHEN1: 1-hydroxyphenanthrene

PHEN2: 2-hydroxyphenanthrene

PHEN3: 3-hydroxyphenanthrene

PHEN4: 4-hydroxyphenanthrene

ΣPHEN: sum of all hydroxyphenanthrene biomarkers

PYR1: 1-hydroxypyrene

SG: specific gravity

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1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous contaminants released by combustion of fossil fuels, vegetation, and tobacco (Phillips, 1999). Many PAHs have been classified as possible carcinogens, and the literature suggests that exposure to PAHs may lead to fetal growth restriction (Bulanda & Janoszka, 2022; Choi et al., 2006; MoghaddamHosseini et al., 2023). Apart from cigarette smoke, occupational exposures, and air pollution, diet is a major route for PAH exposure (Domingo & Nadal, 2015).

Human foods may be contaminated by PAHs during farming processes through PAHs in soil or water (Sampaio et al., 2021), but the main source is from high-temperature food processing like grilling, smoking, and barbecuing, which has been shown to produce high levels of PAHs in foods (Dyremark, 1995; Knize et al., 1999).

While dietary exposure to PAHs may depend on the consumption of multiple food groups, studies have suggested that meats contain high levels of PAHs (Hamidi et al., 2022; Martorell et al., 2012). For example, pregnant women from Southwest Iran had increased blood serum PAH levels with higher meat intake (Khalili Doroodzani et al., 2021). On the other hand, multiple studies have found that vegetables typically have lower levels of PAHs when compared to other food groups (Paris et al., 2018), and some studies in adults found that higher vegetable intake lowers levels of urinary PAH biomarkers (Bulanda & Janoszka, 2022; Fernández et al., 2021; Jain, 2020).

Very few studies have evaluated the relationship between diet and urinary PAH biomarkers in pregnant women (Luo et al., 2022; Zhu et al., 2022). Here we are relying on three different diet indices (HEI-2015, aMED, AHEI-P) to evaluate maternal dietary patterns as they may relate

to PAH exposure. We also consider meat and vegetables, as it is important to assess both diet patterns and components to be able to give dietary advice given to pregnant women.

2. Methods

2.1 Study population

The current study uses data collected from the Imaging Innovations for Placental Assessment in Response to Environmental Exposures (PARENTs), a cohort study of 199 pregnant women who gave birth at the University of California Los Angeles (UCLA). The PARENTs study recruited women with singleton births during early pregnancy from antenatal clinics at UCLA from 2016 to 2019. The purpose of this study was to determine whether multiparametric MRI imaging of the placenta could help predict adverse pregnancy outcomes due to ischemic placental disease (Janzen et al., 2022). Eligibility criteria for enrollment into the study included having a viable singleton with known dating by obstetrical criteria and having the ability and willingness to provide informed consent to undergo placental imaging by MRI and study protocol (Janzen et al., 2022). Women were excluded if they were <18 years of age, if there was known fetal malformation or chromosomal abnormalities at time of enrollment, if they had twin pregnancies, or if they planned to terminate the pregnancy (Janzen et al. 2022).

We collected PAH biomarkers from 159 women and dietary data from 148 women. One woman reporting extremely low caloric intake (<500 kcal/day) was excluded from analysis. A total of 125 (62.8%) out of 199 women enrolled in the PARENTs study had exposure and outcome data and formed our analytical sample.

2.2 Exposure assessment

Diet was evaluated in mid-pregnancy by the Diet History Questionnaire II (DHQ II), a food frequency questionnaire (FFQ) (National Cancer Institute, Applied Research Program, 2005). The DHQ II was administered to each PARENTs participant at one time (between 19-22 weeks of pregnancy), collecting self-reported usual food consumption over the past month. The dietary data was processed using Diet*Calc Analysis Software version 1.4.3 (National Cancer Institute, Applied Research Program, 2005) to estimate food category and nutrient intake. Total meat intake was defined as reporting beef, pork, veal, lamb, and game protein foods and cured meats included frankfurters, sausages, and luncheon meats comprising of beef, pork, or poultry (Bowman et al., 2020). Total vegetable intake included any vegetables excluding legumes, and dark green vegetables included arugula, basil, beet greens, bitter melon leaves, broccoli, Chinese cabbage, chrysanthemum garland, chard, cilantro, collards, cress, dandelion greens, kale, lambsquarters, lettuce, mustard cabbage, mustard greens, parsley, poke greens, spinach, turnip greens, and watercress (Bowman et al., 2020). We summarized meat (total meat and cured meats) and vegetables (total vegetables and dark-green vegetables) consumption as ounce or cup equivalents per day, which is consistent with the Dietary Guidelines for Americans (U.S. Department of Agriculture, 2023). Each participant's meat and vegetable intake was also classified as "high" or "low" using the sample median as the cut point.

DHQ II data was also used to calculate three dietary indices: the Healthy Eating Index - 2015 (HEI-2015), the Alternate Mediterranean Diet (aMED), and the Alternate Healthy Eating Index for Pregnancy (AHEI-P) (Krebs-Smith et al., 2018; Onvani et al., 2017; Trichopoulou et al., 2003). Alcohol was excluded from the scoring methods to make the scales applicable to pregnant women. For all three indices, a higher score indicates higher adherence to the respective dietary pattern.

2.3 Covariate assessment

Covariate data was collected via telephone interviews during pregnancy. Potential confounders were selected through a literature review on PAHs and diet (Cathey et al., 2018; Ferguson et al., 2017; John et al., 2022; Stephens et al., 2017) and included age (years), race/ethnicity (White/non-White), and pre-pregnancy BMI (kg/m^2).

2.4 Outcome assessment

2.4.1 PAH biomarkers from urine samples

Urine samples were collected up to three times throughout pregnancy, and these samples were analyzed for PAH biomarkers. All samples were processed and analyzed at the National Exposure Assessment Laboratory at Emory University. Urine samples for each participant were categorized by time of collection, that is during the mother's first, second, or third trimester (≤13 weeks, 14-27 weeks, and ≥28 weeks, respectively). If an individual had two samples taken during the same trimester we averaged the biomarker measures from both samples. The PAHs (ng/L) measured included 2-hydroxyfluorene + 3-hydroxyfluorene (FLUO2FLUO3), 1-hydroxyphenanthrene (PHEN1), 2-hydroxyphenanthrene (PHEN2), 3-hydroxyphenanthrene (PHEN3), 4-hydroxyphenanthrene (PHEN4), 2-hydroxynaphthalene (NAP2), and 1-hydroxypyrene (PYR1). These hydroxylated PAHs are accepted as biomarkers of fluorene, phenanthrene, naphthalene, and pyrene exposure, respectively (Yang et al., 2021).

Samples with biomarker measurements below the detection limit were substituted with a surrogate value of $LOD/\sqrt{2}$, where LOD is the level of detection, to aid with logarithm

transformation (Hornung & Reed, 1990). This method was considered acceptable as less than ten percent of samples had measurements below the detection limits.

2.4.2 Standardizing the PAH biomarkers

Specific gravity was used to standardize all PAH biomarkers to account for the hydration status of the participant at the time of sampling. Specific gravity was measured for all urine samples with a Reichert AR200 refractometer. Samples with specific gravity ≤1 were excluded from analysis as this indicates a sample density less than that of water.

Specific gravity (SG)-standardized biomarker measures were calculated using the following formula (MacPherson et al., 2018):

$$PAH_{SG,adj}(ng/L) = PAH_i \frac{(SG_{median} - 1)}{(SG_i - 1)}$$

$PAH_{SG,adj}$ is the specific gravity-standardized PAH analyte concentration (ng/L), PAH_i is the observed PAH analyte concentration for an individual, SG_{median} is the median specific gravity (SG) for all study participants, and SG_i is the observed specific gravity of the individual sample.

2.5 Statistical analyses

Descriptive statistics of study participants were conducted using age, parity, maternal race, maternal education, maternal employment status, maternal smoking before pregnancy, and pre-pregnancy BMI as categorical variables. Pearson correlations were calculated for each of the diet measures and the measured PAH biomarkers. For each sampling period (pregnancy trimester), multiple linear regression models were used to estimate the association of the dietary outcome (i.e., diet index score or component) with each urinary PAH biomarker and their combinations, adjusting for maternal age, race/ethnicity, and pre-pregnancy BMI. PAH

biomarker data was natural log transformed to normalize their distributions. All statistical analysis was carried out in R version 4.3.1 (R Core Team, 2023).

3. Results

3.1 Study population characteristics

Demographic information for the entire study sample (n = 125) are reported in Table 1. The average age of participants was 33.5 ± 3.9 years, and most were highly educated (98.4% pursued a degree beyond high school/GED) and employed (85.6%). Almost a third (31.0%) of these pregnant women were overweight or obese before pregnancy started, and about half reported their race as non-Hispanic White, followed by Asian (29.6%), Hispanic (16.0%), Black (5.6%), and American Indian/Alaskan (0.8%). All participants did not report smoking during pregnancy. Only one woman in the PARENTs study had reported smoking during pregnancy but was not included in this analysis. The three dietary indices were moderately to strongly correlated with one another (r = 0.5-0.8, Appendix A.1). Total vegetable intake and dark green vegetable intake showed a moderate positive correlation with aMED and AHEI-P scores (r = 0.3-0.6) but only weakly correlated with HEI-2015 scores (r=0.1-0.2). Furthermore, total meat was weakly correlated with total vegetable intake and dark-green vegetable intake (r = 0.2 and 0.3, respectively), as were the logarithm-transformed urinary PAH biomarkers with each other (r = 0.3-1.0) (Appendix A.1). Log-transformed NAP2 and sum of all PAHs (ΣPAHs) were weakly, negatively correlated with all three diet indices (r = -0.2 to -0.3). The average Healthy Eating Index score for the study sample was higher than the national average (68 vs. 58) (U.S. Department of Agriculture, 2023). Descriptive statistics for the PAH biomarkers by strata of

each covariate can be found in Appendix A.2, and their distributions appear relatively similar across these strata.

Table 1. Descriptive statistics for the study sample (n=125).

Characteristics	N or Mean	% or SD
Maternal age		
Total	33.5	3.9
≤24	2	1.6%
25-29	13	10.4%
30-34	64	51.2%
≥35	46	36.8%
Parity		
0	63	50.4%
1	11	8.8%
>1	51	40.8%
Maternal race		
Asian	37	29.6%
Black, non-Hispanic	7	5.6%
Hispanic	20	16.0%
White, non-Hispanic	60	48.0%
American Indian or Alaskan Native	1	0.8%
Maternal education		
High School Graduate or GED	1	0.8%
Vocational, Technical, Associates or other 2-year degree	4	3.2%
Some College	6	4.8%
Professional degree beyond college	19	15.2%
Bachelor's Degree	43	34.4%
Master's Degree	35	28.0%
Doctoral Degree	16	12.8%
NA	1	0.8%
Employment Status		
Employed	107	85.6%
Student/Other	8	6.4%
Unemployed	8	6.4%
Unemployed & on disability assistance	1	0.8%

NA	1	0.8%
Maternal smoking pre-pregnancy		
Former smoker	19	15.2%
Never smoked	99	79.2%
NA	7	5.6%
Pre-pregnancy BMI		
<18.5	5	4.0%
18.5 - 24.9	81	64.8%
25 - 30	29	23.2%
>30	10	8.0%

3.2 Maternal diet patterns and urinary PAH biomarkers

HEI-2015, aMED, and AHEI-P scores were all negatively associated with each of the trimester-specific urinary PAH biomarkers (Table 2), however not all 95% CIs excluded the null values. Total PAH biomarker concentration (i.e., ∑PAHs, Table 2) decreased, on average, by 20.8 to 25.9% per IQR increase in HEI-2015 score (Table 2). Only the associations for samples taken in the third trimester approached formal statistical significance (B=25.2%; 95% CI: 0.2, 44.0%; $p < 0.05$). A higher HEI-2015 score consistently showed a negative association with each PAH metabolite.

Total urinary PAH biomarker concentration decreased on average by 18.7% to 35.1% per IQR increase in aMED score. Again, only results in the third trimester (35.1%) reached formal statistical significance (95% CI: 15.9%, 50.0%), but negative associations were consistently observed for each of the individual urinary PAHs (Table 2). The negative associations between aMED score and NAP2 reached formal statistical significance ($p < 0.05$) for samples taken during the first and third trimesters (30.8% and 36.3%, respectively).

On average, total PAH concentration detected in the urine decreased by 25.8% to 38.4% for every IQR increase in AHEI-P score, and all individual PAH biomarkers showed a consistent

negative association (Table 2). These associations did not reach formal statistical significance ($p<0.05$). NAP2 concentration in the urine decreased by 27.9 to 38.2% for every IQR increase in AHEI-P score.

Table 2. Percent differences (95% CI) in biomarker concentrations per IQR higher HEI-2015, aMED, and AHEI-P scores.

Dietary Pattern/Index	Trimester 1 (n = 62)	Trimester 2 (n =112)	Trimester 3 (n = 95)
Healthy Eating Index 2015 (HEI-2015)*			
FLUO2FLUO3	-15.4 (-34.6, 9.5)	-12.0 (-28.9, 8.9)	-9.0 (-28.5, 15.9)
NAP2	-25.6 (-52.2, 15.8)	-24.5 (-45.5, 4.7)	-27.1 (-46.6, -0.5)
PHEN1	-20.7 (-39.3, 3.5)	-15.6 (-30.6, 2.5)	-0.7 (-25.0, 31.6)
PHEN2	-16.2 (-35.1, 8.2)	-8.9 (-23.6, 8.7)	0 (-20.1, 25.2)
PHEN3	-15.6 (-33.9, 7.7)	-7.6 (-22.0, 9.5)	2.0 (-19.1, 28.6)
PHEN4	-21.9 (-38.7, -0.5)	-11.9 (-25.9, 4.7)	4.1 (-21.8, 38.4)
PYR1	-17.8 (-39.3, 11.4)	-3.5 (-19.8, 16.1)	-9.6 (-29.5, 16.1)
ΣPHEN**	-19.8 (-36.8, 1.8)	-11.3 (-24.4, 4.2)	0.9 (-19.0, 25.8)
ΣPAHs**	-25.9 (-49.9, 9.5)	-20.8 (-40.4, 5.4)	-25.2 (-44.0, -0.2)
Alternate Mediterranean Diet (aMED)*			
FLUO2FLUO3	-13.6 (-30.1, 6.7)	-19.1 (-32.1, -3.7)	-16.4 (-33.1, 4.4)
NAP2	-30.8 (-51.5, -1.2)	-20.0 (-39.2, 5.2)	-36.3 (-51.9, -15.6)
PHEN1	-11.3 (-29.0, 10.9)	-17.9 (-30.1, -3.6)	-14.7 (-34.2, 10.7)
PHEN2	-13.7 (-30.0, 6.5)	-9.1 (-21.5, 5.3)	-20.4 (-35.1, -2.4)
PHEN3	-14.0 (-29.6, 5.0)	-12.6 (-24.0, 0.6)	-12.0 (-29.0, 9.0)
PHEN4	-14.2 (-29.9, 5.0)	-8.4 (-20.8, 6.0)	5.9 (-18.8, 38.1)
PYR1	-10.5 (-30.4, 15.1)	-9.4 (-22.3, 5.7)	-16.2 (-33.5, 5.4)
ΣPHEN**	-12.8 (-28.5, 6.3)	-12.8 (-23.7, -0.4)	-11.4 (-27.7, 8.6)
ΣPAHs**	-30.5 (-49.2, -5.0)	-18.7 (-36.0, 3.2)	-35.1 (-50.0, -15.9)
Alternate Healthy Eating Index for Pregnancy (AHEI-P)*			
FLUO2FLUO3	-19.2 (-36.1, 2.3)	-14.0 (-28.4, 3.4)	-14.9 (-31.0, 5.1)
NAP2	-38.2 (-58.4, -8.3)	-27.9 (-45.5, -4.6)	-38.2 (-52.4, -19.8)
PHEN1	-17.4 (-35.5, 5.8)	-12.0 (-25.7, 4.3)	-9.1 (-29.0, 16.3)
PHEN2	-17.5 (-34.8, 4.3)	-4.2 (-17.9, 11.6)	-17.0 (-31.6, 0.8)
PHEN3	-20.8 (-36.5, -1.3)	-5.0 (-18.1, 10.1)	-5.9 (-23.2, 15.3)
PHEN4	-25.4 (-40.0, -7.2)	-2.0 (-15.7, 14.1)	11.5 (-13.2, 43.2)
PYR1	-24.5 (-42.6, -0.6)	-5.7 (-19.6, 10.7)	-21.1 (-36.3, -2.2)
ΣPHEN**	-19.1 (-35.1, 0.8)	-6.9 (-19.0, 7.1)	-8.7 (-24.7, 10.7)

ΣPAHs**	-38.4 (-56.4, -13)	-25.8 (-41.9, -5.3)	-37.0 (-50.5, -19.8)

*adjusted for age, BMI, and race/ethnicity
**ΣPHEN: PHEN1+PHEN2+PHEN3+PHEN4, ΣPAHs: sum of all PAH biomarkers

3.3 Meat intake and urinary PAH biomarkers

On average, higher (≥median) total meat intake was associated on average with a 79.8% (95% CI: 0.7, 220.8%) increase in total urinary PAH biomarkers in the first trimester when compared to participants with total meat intake below the median (Table 3). Smaller positive associations were also seen in the second and third trimesters but did not reach formal statistical significance. High total meat intake was associated with higher FLUO2FLUO3 (4.4-39.1%), NAP2 (13.7-93.8%), PHEN2 (7.2-68.5%), PHEN3 (3.4-56.8%), PYR1 (0.9-23.9%), ΣPHEN (2.1-54.2%) concentrations in all three trimesters and increased PHEN1 (2.8-43.6%) and PHEN4 (9.6-61.9%) in two trimesters.

While higher (≥median) cured meat intake was associated with an increase in total urinary PAH biomarker concentration in all three trimesters (14.3-115.5%) when compared to those with cured meat intake below the median, this appeared to be primarily driven by NAP2 concentration, for which increases ranged between 22.9% and 158.4% in all three trimesters (Table 3). Results for the other PAH metabolites were inconsistent for cured meat consumption.

Results from regression models with total and cured meat consumption defined as continuous variables (ounce equivalents per day) were less consistent across all three trimesters, showing both positive and negative associations with the PAH metabolites (Appendix A.3).

3.4 Vegetable intake and urinary PAH biomarkers

On average, higher (≥median) vegetable intake was associated with a 32.4% (95% CI: -1.0, 54.7%) decrease in total PAH biomarkers when compared to women with lower (≤median)

vegetable intake in the third trimester (Table 3). Results were consistent for the second trimester but did not reach formal statistical significance. Overall, higher (≥median) dark-green vegetable consumption was associated with decreased urinary PAH biomarker concentration when compared to individuals with those with dark-green vegetable intake below the median; however, 95% CIs cross the null (Table 3).

Higher (≥median) total vegetable intake was associated with a decrease in FLUO2FLUO3, PHEN2, PHEN3, and ΣPHEN in all three trimesters and for NAP2, PHEN1, PHEN4, and PYR1 in one or two trimesters. Higher (≥median) dark-green vegetable consumption was associated with a decrease in FLUO2FLUO3, PHEN1, PHEN2, PYR1, and ΣPHEN in all three trimesters, and in NAP2, PHEN3, and PHEN4 in one or two trimesters, when compared to individual with low dark-green vegetable consumption.

Results were similar, showing inverse associations between vegetable intake and PAHs, when total and dark-green vegetable consumption was defined as a continuous variable (cup equivalents per day) (Appendix A.3).

Table 3. Percent differences (95% CI) in biomarker concentrations in individuals with higher (≥median) vs. lower total (≤median) total meat consumption, cured meat consumption, total vegetable consumption, and dark-green vegetable consumption.

Variable	Trimester 1 (n = 62)	Trimester 2 (n =112)	Trimester 3 (n = 95)
Total meat (high vs. low)*			
FLUO2FLUO3	39.1 (-5.2, 104.1)	4.4 (-22.3, 40.4)	7.4 (-23.2, 50.1)
NAP2	93.8 (1.0, 272.2)	13.7 (-28.0, 79.6)	37.8 (-10.8, 112.8)
PHEN1	43.6 (-3.7, 114.1)	2.8 (-21.8, 35)	-1.4 (-33.2, 45.5)
PHEN2	68.5 (17.0, 142.8)	7.2 (-16.0, 36.9)	14.7 (-15.8, 56.3)
PHEN3	56.8 (10.1, 123.3)	3.4 (-18.3, 30.8)	3.1 (-25.2, 42.0)
PHEN4	61.9 (13.6, 130.8)	9.6 (-13.8, 39.5)	-4.0 (-35.3, 42.5)
PYR1	23.9 (-21.8, 96.2)	2.9 (-20.3, 33)	0.9 (-28.7, 42.6)
ΣPHEN**	54.2 (8.6, 118.9)	5.1 (-15.9, 31.5)	2.1 (-24.7, 38.5)

ΣPAHs**	79.8 (0.7, 220.8)	7.0 (-28.2, 59.4)	31.4 (-12.3, 96.9)
Cured meat (high vs. low)*			
FLUO2FLUO3	-2.2 (-33.7, 44.4)	-2.5 (-27.9, 31.7)	13.6 (-19.3, 59.9)
NAP2	158.4 (39.0, 380.3)	22.9 (-22.7, 95.3)	53.2 (-1.4, 138.0)
PHEN1	-6.0 (-37.4, 41.3)	-16.1 (-36.3, 10.5)	-31.5 (-53.6, 1.1)
PHEN2	2.1 (-30.6, 50.4)	-8.2 (-28.4, 17.7)	-5.8 (-31.4, 29.3)
PHEN3	-1.8 (-32.1, 42.1)	-11.4 (-30.2, 12.5)	-5.2 (-31.6, 31.5)
PHEN4	27.5 (-11.8, 84.1)	-7.4 (-27.5, 18.4)	-27.6 (-51.3, 7.9)
PYR1	-20.9 (-49.8, 24.7)	-11.1 (-31.5, 15.2)	-7.3 (-34.9, 32.0)
ΣPHEN**	0.3 (-30.4, 44.5)	-12.8 (-30.4, 9.4)	-23.0 (-43.3, 4.5)
ΣPAHs**	115.5 (23.3, 276.6)	14.3 (-23.8, 71.4)	41.3 (-6.3, 113.2)
Total vegetables (high vs. low)*			
FLUO2FLUO3	-0.7 (-33.0, 47.1)	-23.9 (-43.3, 2.1)	-12.5 (-37.4, 22.4)
NAP2	39.2 (-28.8, 172.1)	2.3 (-35.5, 62.2)	-31.8 (-55.8, 5.2)
PHEN1	0.2 (-33.6, 51.2)	-29.5 (-46.0, -8.0)	-24.4 (-48.6, 11.2)
PHEN2	-1.6 (-33.4, 45.5)	-18.9 (-36.4, 3.4)	-23.0 (-43.3, 4.6)
PHEN3	-3.6 (-33.6, 40.1)	-12.6 (-31, 10.6)	-10.4 (-34.9, 23.4)
PHEN4	0.5 (-31.1, 46.6)	-14.3 (-32.7, 9.1)	-0.6 (-33.1, 47.6)
PYR1	5.6 (-33.6, 67.9)	-18.1 (-36.5, 5.7)	-19.6 (-43.0, 13.5)
ΣPHEN**	-0.7 (-31.3, 43.7)	-21.5 (-37.0, -2.1)	-22.0 (-42.3, 5.3)
ΣPAHs**	26.5 (-30.4, 129.8)	-8.0 (-38.5, 37.4)	-32.4 (-54.7, 1.0)
Dark-green vegetables (high vs. low)*			
FLUO2FLUO3	-24.7 (-48.8, 10.6)	-12.0 (-34.5, 18.3)	-9.0 (-35.1, 27.7)
NAP2	-2.0 (-50.0, 92.3)	11.8 (-29.3, 76.7)	-27.5 (-53.3, 12.7)
PHEN1	-27.7 (-51.6, 8.0)	-14.5 (-34.9, 12.2)	-24.5 (-48.9, 11.4)
PHEN2	-19.6 (-45.3, 18.2)	-5.3 (-25.9, 21.0)	-7.1 (-32.1, 27.1)
PHEN3	-20.6 (-45.0, 14.6)	2.5 (-19.1, 29.8)	-7.5 (-33.1, 27.8)
PHEN4	-7.4 (-36.4, 34.9)	0.5 (-21.1, 28.0)	5.3 (-29.4, 57.0)
PYR1	-28.3 (-54.4, 12.9)	-5.8 (-27.1, 21.7)	-21.1 (-44.2, 11.7)
ΣPHEN**	-22.4 (-46.0, 11.4)	-6.6 (-25.3, 16.9)	-13.7 (-36.5, 17.2)
ΣPAHs**	-11.5 (-51.3, 60.7)	2.5 (-31.3, 53.0)	-26.8 (-51.3, 10.0)

*adjusted for age, BMI, and race/ethnicity

**ΣPHEN: PHEN1+PHEN2+PHEN3+PHEN4, ΣPAHs: sum of all PAH biomarkers

4. Discussion

We investigated the relationship between maternal diet and urinary PAH biomarkers in pregnant women who gave birth at UCLA between 2016 and 2019. Lower urinary PAH

biomarker levels were associated with better adherence to a Mediterranean dietary pattern (i.e., aMED score) and the Dietary Guidelines for Americans (i.e., HEI-2015 and AHEI-P scores). Higher (≥median) total and cured meat consumption generally increased urinary PAH biomarkers, while higher total and dark-green vegetable consumption decreased urinary PAHs.

Diet composition and quality can have important implications on PAH exposure and metabolism. Once ingested, PAHs are believed to undergo metabolism by cytochrome P450 enzymes (CYP) (Jacob & Seidel, 2002). This process forms the hydroxylated metabolites excreted in urine (Jacob & Seidel, 2002; Penning, 1993). A diet rich in PAHs is associated with higher levels of metabolites detected in the urine (Jacob & Seidel, 2002). On the other hand, cruciferous vegetables have been associated with induction of CYP *in vivo* (Eagles et al., 2020; Ioannides, 1999). Increased CYP activity could aid in the efficient metabolism and excretion of PAHs after ingestion (Shimada, 2006), and could theoretically result in lower levels of urinary PAH biomarkers due to faster excretion.

4.1 Diet patterns and PAH biomarkers in the urine

Higher HEI-2015 and AHEI-P scores were associated with lower levels of urinary PAH biomarkers. This is consistent with results from a study of 251 working adults in Japan, which found evidence to suggest that an increase in the ratio of meat/fish to vegetable intake was associated with PYR1 levels (Kawamoto et al., 2007). A study of 110 lactating women suggested better adherence to a Mediterranean diet was associated with lower levels of naphthalene metabolites in their urine (Fernández et al., 2021), corroborating our own results for pregnant women as we also found a higher Mediterranean diet score to be associated with decreased urinary PAH biomarkers.

The HEI-2015 and Alternate Healthy Index for Pregnancy (AHEI-P) are based on the Dietary Guidelines for Americans (Krebs-Smith et al., 2018; Onvani et al., 2017; U.S. Department of Agriculture, 2023). The AHEI-P is specific to pregnancy and may better reflect diet quality in our targeted women. The aMED score was modified from the Mediterranean diet score to include components specific to vegetables, excluding potato products, as well as red and processed meats (Fung et al., 2005; Trichopoulou et al., 2003). This may explain why the AHEI-P and aMED scores, which include scoring components specific to red meat consumption, reflect more dramatic changes in the measured PAH biomarkers.

4.2 Dietary components and PAH biomarkers in the urine

We found that total meat consumption was associated with higher levels of all PAH biomarkers measured in urine, which is consistent with the current literature on meat consumption and PAHs. In a sample of Chinese pregnant women, Luo et al., 2022 report a diet high in red meat, poultry, and aquatic products to be associated with higher levels of PAH metabolites detected in the urine. Among a sample of U.S. adults, consumption of red and processed meats was associated with higher levels of fluorene, pyrene, and phenanthrene biomarkers in the urine (Jain, 2020).

Multiple studies have found that grilled and processed meats have high levels of naphthalene, phenanthrene, and pyrene (Alomirah et al., 2011; Falcó et al., 2003). However, our study only found an increase in urinary 2-hydroxynaphthalene, a metabolite of naphthalene, among individuals with higher (≥median) cured meat consumption (22.9-158.4%) for all three trimesters.

Our study found higher (≥median) vegetable consumption was associated with decreased levels of PAH biomarkers (FLUO2FLUO3, NAP2, PHEN1, PHEN2, PHEN3, PHEN4, PYR1, ΣPHEN, and ΣPAHs) measured in the urine, corroborating previous studies reporting decreased naphthalene metabolites in the urine (Fernández et al., 2021). In our study, we also found higher dark-green vegetable consumption was also associated with decreased levels of the measured PAH biomarkers.

Results were similar for total meat, total vegetable, and dark-green vegetable consumption when we used ounce or cup equivalents per day. However, the positive association between cured meat consumption and urinary PAH biomarkers only remained consistent for NAP2 and the sum of all measured PAH biomarkers (ΣPAHs).

4.3 Strengths and limitations

Our study has multiple strengths. First, we measured PAH metabolites in the urine, which may better reflect overall PAH exposure compared to measuring PAHs in food samples. Second, we used three validated diet indices to evaluate dietary patterns in addition to analyzing individual components. Calculated diet indices may better reflect a healthy or higher quality diet (Ocké, 2013) in ways that individual food components cannot.

This study has some limitations. Our study assumes a stable diet throughout pregnancy. Diet was assessed at one time point during mid-pregnancy and may not accurately reflect diet during early or late pregnancy. Although we found consistent associations throughout all three trimesters, our exposure assessment may be subject to measurement error, especially during the first trimester, as women may eat differently before knowing they are pregnant (Forbes et al., 2018). In addition, the accuracy of diet data collected via FFQ may be limited due to participant

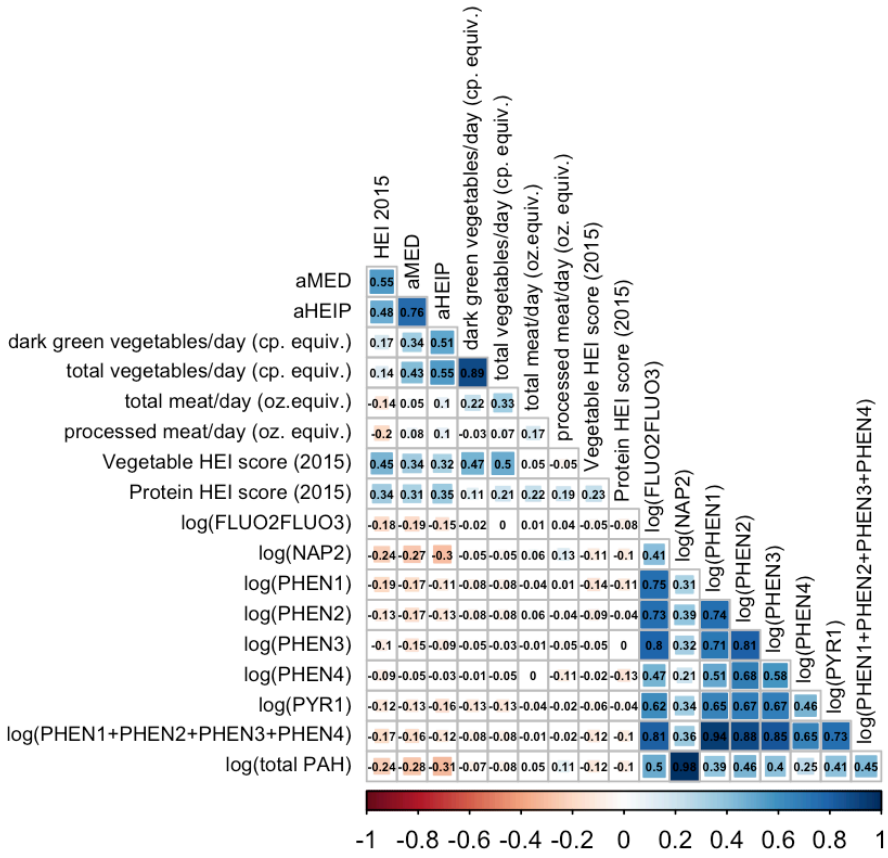
recall error and fatigue (Biró et al., 2002; Shim et al., 2014). Results for samples taken in the first trimester were limited by sample size (n = 62) compared to the other two trimesters. Further studies with a larger sample size are required.

5. Conclusion

Our study found evidence to suggest that certain dietary patterns, as reflected by HEI-2015, aMED, and AHEI-P scores, may be associated with decreased PAH exposure. Furthermore, higher meat consumption may increase PAH exposure, while higher vegetable consumption may reflect decreased PAH exposure and burden. We believe that urinary PAH metabolites reflect overall exposure, and a healthier diet may contribute to decreased levels of urinary PAH metabolites. Additional research is needed to improve diet recommendations for pregnant women.

Appendix

A.1. Correlation matrix of exposure and outcome variables.



A.2. Summary statistics of PAHs by confounder stratum.

(a)

Variable	Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
Age (in years)						
FLUO2FLUO3						
<35 (n = 76)	2.33	4.16	4.55	4.62	5.05	6.67
≥35 (n = 46)	2.94	4.23	4.78	4.84	5.32	7.90
NAP2						
<35 (n = 76)	4.44	7.10	7.92	7.92	8.62	11.44
≥35 (n = 46)	3.48	7.27	7.87	8.04	8.71	11.40

PHEN1						
<35 (n = 76)	1.65	3.71	4.20	4.23	4.69	6.61
≥35 (n = 46)	2.39	3.76	4.36	4.40	4.89	7.42
PHEN2						
<35 (n = 76)	1.07	2.93	3.27	3.33	3.72	5.66
≥35 (n = 46)	1.78	2.94	3.34	3.42	3.79	6.21
PHEN3						
<35 (n = 76)	1.56	2.82	3.20	3.25	3.65	4.86
≥35 (n = 46)	1.88	2.79	3.19	3.30	3.64	5.93
PHEN4						
<35 (n = 76)	1.05	2.30	2.77	2.78	3.22	5.28
≥35 (n = 46)	1.30	2.25	2.67	2.77	3.16	5.42
PYR1						
<35 (n = 76)	0.51	3.45	3.85	3.92	4.38	6.62
≥35 (n = 46)	2.08	3.34	3.86	3.89	4.27	7.27
∑PHEN						
<35 (n = 76)	3.61	4.54	4.94	5.00	5.38	7.11
≥35 (n = 46)	3.70	4.56	5.03	5.09	5.42	7.78
∑PAH						
<35 (n = 76)	5.94	7.39	8.04	8.09	8.70	11.45
≥35 (n = 46)	5.36	7.45	8.04	8.20	8.76	11.41
Race/ethnicity						
FLUO2FLUO3						
White (n = 60)	2.89	4.33	4.83	4.91	5.44	7.90
non-White (n = 65)	2.33	4.11	4.50	4.50	4.99	5.95
NAP2						
White (n = 60)	3.48	7.12	7.99	7.93	8.74	11.44
non-White (n = 65)	5.54	7.29	7.83	7.99	8.61	11.40
PHEN1						
White (n = 60)	1.77	3.96	4.47	4.50	4.97	7.42
non-White (n = 65)	1.65	3.61	4.12	4.10	4.56	6.18
PHEN2						
White (n = 60)	1.07	2.93	3.35	3.48	3.91	6.21
non-White (n = 65)	1.59	2.95	3.23	3.25	3.57	5.55
PHEN3						
White (n = 60)	1.77	2.81	3.28	3.43	3.96	5.93
non-White (n = 65)	1.56	2.78	3.17	3.11	3.49	4.67
PHEN4						
White (n = 60)	1.05	2.21	2.79	2.84	3.34	5.42

non-White (n = 65)	1.19	2.30	2.71	2.71	3.10	4.96
PYR1						
White (n = 60)	2.37	3.44	3.95	4.01	4.39	7.27
non-White (n = 65)	0.51	3.37	3.78	3.81	4.26	5.80
∑PHEN						
White (n = 60)	3.61	4.64	5.07	5.19	5.56	7.78
non-White (n = 65)	3.73	4.47	4.91	4.88	5.21	6.78
∑PAH						
White (n = 60)	5.36	7.36	8.09	8.15	8.83	11.45
non-White (n = 65)	5.96	7.42	7.97	8.12	8.70	11.41
Pre-pregnancy BMI						
FLUO2FLUO3						
<25 kg/m^2 (n = 86)	2.33	4.11	4.54	4.61	5.03	6.67
≥25 kg/m^2 (n = 39)	2.89	4.46	4.77	4.90	5.28	7.90
NAP2						
<25 kg/m^2 (n = 86)	3.48	7.08	7.79	7.79	8.49	11.44
≥25 kg/m^2 (n = 39)	5.90	7.44	8.40	8.34	9.38	11.40
PHEN1						
<25 kg/m^2 (n = 86)	1.65	3.62	4.17	4.19	4.69	6.67
≥25 kg/m^2 (n = 39)	2.87	4.08	4.40	4.53	4.89	7.42
PHEN2						
<25 kg/m^2 (n = 86)	1.59	2.90	3.23	3.31	3.67	5.66
≥25 kg/m^2 (n = 39)	1.07	3.02	3.42	3.48	3.82	6.21
PHEN3						
<25 kg/m^2 (n = 86)	1.56	2.77	3.17	3.22	3.62	4.92
≥25 kg/m^2 (n = 39)	1.77	2.92	3.27	3.36	3.69	5.93
PHEN4						
<25 kg/m^2 (n = 86)	1.05	2.29	2.73	2.75	3.18	5.28
≥25 kg/m^2 (n = 39)	1.30	2.32	2.72	2.82	3.21	5.42
PYR1						
<25 kg/m^2 (n = 86)	0.51	3.39	3.83	3.88	4.30	6.62
≥25 kg/m^2 (n = 39)	2.08	3.48	3.98	3.98	4.46	7.27
∑PHEN						
<25 kg/m^2 (n = 86)	3.70	4.49	4.91	4.96	5.38	7.16
≥25 kg/m^2 (n = 39)	3.61	4.73	5.09	5.19	5.44	7.78
∑PAH						
<25 kg/m^2 (n = 86)	5.36	7.34	7.92	7.98	8.57	11.45
≥25 kg/m^2 (n = 39)	6.11	7.64	8.48	8.48	9.41	11.41

A.3. Percent differences (95% CI) in PAH biomarkers for continuous outcome variables.

Variable	Trimester 1 (n = 62)	Trimester 2 (n =112)	Trimester 3 (n = 95)
Total meat (oz equiv. per day)*			
FLUO2FLUO3	9.7 (-16.9, 44.7)	2.8 (-14.6, 23.8)	-10.4 (-28.2, 11.7)
NAP2	45.6 (-8.7, 132.4)	-5.7 (-29.2, 25.7)	10.2 (-17.6, 47.3)
PHEN1	7.1 (-19.9, 43.1)	-1.3 (-16.9, 17.1)	-20.1 (-38.0, 2.9)
PHEN2	24 (-5.3, 62.5)	2.4 (-12.2, 19.4)	-2.9 (-21.0, 19.2)
PHEN3	9.2 (-16.1, 42)	-2.4 (-15.8, 13.1)	-6.7 (-24.5, 15.3)
PHEN4	29.5 (0.1, 67.5)	-2.7 (-16.4, 13.2)	-12.3 (-32.4, 13.7)
PYR1	2.0 (-26.5, 41.5)	-2.1 (-16.6, 15)	-14.7 (-32.0, 7.0)
ΣPHEN**	13.9 (-12.0, 47.6)	-1.2 (-14.2, 13.7)	-12.1 (-28.0, 7.3)
ΣPAHs**	35.9 (-10.4, 106.1)	-7.1 (-27.7, 19.3)	6.4 (-18.7, 39.4)
Cured meat (oz equiv. per day)*			
FLUO2FLUO3	-27.3 (-56.6, 21.6)	-4.6 (-39.5, 50.3)	-4.1 (-41.9, 58.1)
NAP2	25.2 (-48.8, 205.9)	9.2 (-46.0, 120.5)	14.5 (-40.5, 120.6)
PHEN1	-31.9 (-60.2, 16.3)	4.4 (-31.4, 58.8)	-30.7 (-61.0, 23.1)
PHEN2	-25.8 (-55.5, 23.8)	-12.1 (-39.6, 27.9)	-20.1 (-49.6, 26.7)
PHEN3	-31.9 (-58.0, 10.6)	-9.4 (-36.9, 30.1)	-9.7 (-43.9, 45.5)
PHEN4	-18.5 (-50.4, 34.0)	-23.6 (-47.1, 10.3)	-39.1 (-65.9, 8.7)
PYR1	-25.9 (-59.7, 36.4)	-4.6 (-35.6, 41.5)	-7.1 (-44.5, 55.7)
ΣPHEN**	-28.7 (-55.9, 15.4)	-5.0 (-32.6, 34.0)	-24.2 (-51.7, 18.9)
ΣPAHs**	16.4 (-47.4, 157.5)	6.2 (-42.5, 96.2)	7.8 (-41.3, 98.1)
Total vegetables (cup equiv. per day)*			
FLUO2FLUO3	-1.5 (-14.7, 13.7)	-4.8 (-15.6, 7.3)	-6.9 (-21.5, 10.4)
NAP2	6.1 (-17.1, 35.8)	-1.8 (-18.4, 18.2)	-18.4 (-34.6, 1.7)
PHEN1	-8.8 (-21.4, 5.7)	-6.5 (-16.3, 4.4)	-16.2 (-31.1, 1.9)
PHEN2	-6.1 (-18.5, 8.2)	-4.1 (-13.1, 5.9)	-11.7 (-24.5, 3.3)
PHEN3	-8.1 (-19.7, 5.2)	-2.2 (-11.1, 7.6)	-3.9 (-18.4, 13.1)
PHEN4	-8.5 (-20.1, 4.9)	-3.3 (-12.3, 6.6)	-0.1 (-18.3, 22.3)
PYR1	-6.8 (-21.2, 10.3)	-4.5 (-13.9, 5.9)	-22.0 (-34.1, -7.6)
ΣPHEN**	-8.2 (-19.6, 4.8)	-4.3 (-12.5, 4.8)	-12.1 (-24.6, 2.4)
ΣPAHs**	1.9 (-18.2, 26.9)	-4.7 (-18.9, 12.1)	-18.8 (-33.8, -0.5)
Dark-green vegetables (cup equiv. per day)*			
FLUO2FLUO3	-5.5 (-28.8, 25.5)	-6.2 (-25.8, 18.6)	-10.6 (-35.5, 23.8)
NAP2	15.1 (-29.2, 87.1)	2.7 (-28.6, 47.7)	-33.7 (-56.4, 0.8)

PHEN1	-16.7 (-37.8, 11.7)	-8.3 (-26.2, 13.7)	-20.2 (-45.2, 16.1)
PHEN2	-12.8 (-34.0, 15.4)	-6.8 (-23.2, 13.2)	-11.8 (-34.8, 19.1)
PHEN3	-14.3 (-34.3, 11.8)	-2.9 (-19.5, 17)	-6.8 (-31.7, 27.2)
PHEN4	-15.2 (-35.2, 10.9)	-0.8 (-18.1, 20.1)	15.3 (-21.4, 69.1)
PYR1	-16.8 (-40.2, 15.9)	-6.5 (-23.7, 14.5)	-29.0 (-48.9, -1.3)
ΣPHEN**	-15.4 (-35.0, 9.9)	-5.4 (-20.7, 13.0)	-13.9 (-35.9, 15.6)
ΣPAHs**	5.4 (-31.6, 62.5)	-3.3 (-29.6, 32.8)	-33.1 (-54.6, -1.3)

*adjusted for age, BMI, and race/ethnicity

**ΣPHEN: PHEN1+PHEN2+PHEN3+PHEN4, ΣPAHs: sum of all PAH biomarkers

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