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Polycyclic aromatic hydrocarbon exposure during pregnancy and changes in umbilical renal function

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Abstract

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants with significant adverse effects on human health, particularly concerning fetal development during pregnancy. This study investigates the relationship between maternal exposure to particulate matter-bound (PM-bound) PAHs and potential alterations in fetal renal function. A cross-sectional investigation was conducted on 450 mother-pair newborns from June 2019 to August 2021. Exposure to PM-bound PAHs was estimated at the residential address using spatiotemporal models based on data from 30 monitoring stations across the study area. Umbilical cord blood samples were collected post-delivery for biochemical analysis of renal function markers, including creatinine (Cr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). Multivariable regression models were used to assess the relationship between exposure to each PAHs compound and fetal renal function. Moreover, the mixture effects of exposure to PAHs on fetal renal function were assessed using quantile g-computation analysis. Increased concentrations of various PAH compounds at the residential address correlated with raised levels of umbilical BUN and Cr, suggesting potential renal impairment. Notably, exposure to certain PAHs compounds demonstrated statistically negative significant associations with eGFR levels. An increment of one quartile in exposure to PAHs mixture was correlated with a rise of 1.08 mg/dL (95% CI 0.04, 2.11, $p=0.04$) and 0.02 mg/dL (95% CI −0.00, 0.05, $p=0.05$) increase in BUN and Cr, respectively. Moreover, a one-quartile increase in PAHs mixture exposure was associated with −1.09 mL/min/1.73 m^2 (95% CI −2.03, −0.14, $p=0.02$) decrease in eGFR. These findings highlight the potential impact of PAH exposure on fetal renal function and underscore the importance of considering environmental exposures in assessing neonatal renal health outcomes.

Keywords Fetus, Kidney, Maternal exposure, Neonate, Environmental exposures

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Introduction

Particulate matter (PM) is a complex mixture of solid and liquid particles suspended in the air, originating from various natural and anthropogenic sources such as vehicle emissions, industrial processes, and agricultural activities [50]. PM can vary in size, with fine particles ($PM_{2.5}$) and ultrafine particles ($PM_{0.1}$) being of particular concern due to their ability to penetrate deep into the respiratory system and enter the bloodstream. These particles can serve as carriers for a wide range of materials and compounds, including polycyclic aromatic hydrocarbons (PAHs) [25]. PAHs are environmental contaminants that primarily originate from the incomplete combustion of organic substances like fossil fuels, tobacco, and biomass [17, 23, 32, 49]. These compounds are pervasive in urban environments, and their widespread presence in air, soil, and water has raised significant concerns due to their adverse effects on human health [52]. PAHs consist of multiple fused aromatic rings, and their complex chemical structure contributes to their persistence and bioaccumulation in various environmental compartments [2]. The human health effects of PAH exposure have been a subject of extensive research. Inhalation, ingestion, and dermal contact are common routes through which individuals are exposed to PAHs [27]. Upon exposure, these compounds undergo metabolic activation, forming reactive intermediates that can bind to cellular DNA, leading to genotoxic effects [57]. Besides, PAHs have been implicated in endocrine disruption, oxidative stress, and inflammatory responses, with potential links to various adverse health outcomes, including respiratory diseases and cancer [32, 54].

Throughout pregnancy, the developing fetus is notably susceptible to environmental influences, and maternal contact with PAHs has been linked to various negative consequences [29, 32, 35]. PAHs' lipophilicities properties facilitate their passage through the placental barrier, thereby subjecting the developing fetus to these environmental pollutants [12, 21]. Studies have linked maternal PAH exposure to low birth weight, preterm birth, and developmental issues, emphasizing the need for a comprehensive understanding of the potential risks posed by these pollutants during gestation [32, 47, 56]. Renal development in the fetus is a crucial process integral to overall fetal growth and well-being [40]. The umbilical cord serves as the lifeline for nutrient transfer, waste elimination, and communication between the fetus and the maternal environment [9]. Umbilical renal enzymes play a pivotal role in these processes, contributing to metabolic functions that are essential for maintaining fetal renal homeostasis [6, 28, 33, 37]. Despite the critical nature of these enzymes, research investigating the impact of environmental pollutants [26, 39, 41], particularly PAHs, on renal function remains limited [16, 48, 58] with no study on the association between exposure to PAHs during pregnancy and fetal renal function.

This study aims to fill this void by investigating the complex association between PAH exposure during pregnancy and potential changes in fetal renal function. By unravelling the effects of PAHs on fetal renal function, the research aims to provide valuable insights into the complex interplay between environmental exposures and the developing fetus. Such knowledge is essential for informing public health strategies and interventions aimed at mitigating the potential risks associated with PAH exposure during pregnancy, ultimately contributing to the well-being of both mothers and their developing infants.

Methods

Population and study setting

This cross-sectional study was conducted in Sabzevar, located in the northwest region of the Khorasan-Rezavi Province, Iran. Sabzevar has a population of around 250,000, with women comprising nearly half of the population. The city experiences an arid climate, with an average annual rainfall of approximately 170 mm, mainly concentrated during the winter season. The city faces challenges such as heavy traffic and air pollution due to the presence of the main east-to-west highway and narrow roads influenced by its historical context [1].

The study focused on pregnant women accessing care at the sole maternity hospital in Sabzevar, namely Shahidan Mobini, for deliveries spanning from June 2019 to August 2021. The study objectives and procedures were communicated to mothers visiting the hospital, with approximately 1500 pregnant women informed during the study duration. Ultimately, 450 eligible women, fulfilling inclusion criteria such as having a normal gestational age (37–42 weeks), undergoing a normal vaginal delivery, having no pregnancy complications (e.g., hypertension, gestational diabetes mellitus, and preeclampsia), being non-smokers and non-alcohol consumers, not relocating during pregnancy, and residing in Sabzevar for at least the past year, consented and participated in the study. Lifestyle and sociodemographic data were collected through face-to-face interviews conducted on the day following delivery. Neighborhood socioeconomic status (SES) indicators including unemployed percent per census tract and Illiterate percent per census tract were calculated based on the population layer of Sabzevar, provided by the Statistical Center of Iran according to the last census in Iran (i.e., 2016) in GIS software version 10.8.1 (ESRI ArcGIS Desktop 10.8.1).

Assessment of exposure

To estimate the concentration of PM-bound PAH compounds at residential addresses, the mothers' home addresses were geocoded using a GPS device (Garmin eTrex 22x). It should be noted that none of the participants changed their residence during the entire pregnancy period. Exposure to PM-bound PAHs at residential homes was estimated using the ordinary kriging (OK) models developed for the study area. This involved developing models based on data collected from 30 strategically positioned monitoring stations across Sabzevar. Thirty monitoring stations were set up across Sabzevar, covering various land use types and traffic volumes (one monitoring station per 1 km^2 of study area). PM-bound PAHs were collected using passive samplers over three months and analyzed based on ng/m^3 using established methods. After collection, samples were stored and underwent extraction using dichloromethane solvent. Gas chromatography with a mass spectrometer detector (GC/MS) was used for the detection of these compounds. Detailed information on the measurements of PM-bound PAHs can be found elsewhere [27]. 15 PAH compounds, namely benzo[a]pyrene (BaP), chrysene (Chr), acenaphthene (Ace), naphthalene (NapH), fluoranthene (F), indeno[1,2,3-cd]pyrene (IcdPy), benzo[g,h,i] perylene (BghiP), anthracene (Anth), fluorene (Fl), dibenzo[a,h]anthrancene (DbahA), benzo[a]anthracene (BaA), phenanthrene (Phen), benzo[b]fluoranthene (BbF), acenaphthylene (Ac), and Pyrene (Py) were measured. Various metrics, such as total high molecular weight PAHs (HMW-PAHs), total 3,4,5, and 6-ring PAHs, total low molecular weight PAHs (LWM-PAHs), and total PAHs, were calculated using the levels of the 15 PAHs measured by GC/MS. The OK models had a resolution of 12 m and demonstrated robust performance, indicating their ability to predict 0.74 to 0.82 variations in PAH-bound PM across the study area. These models stand as crucial tools for accurately estimating residential exposure to PM-bound PAHs, providing a foundation for further exploration of the potential health implications associated with these environmental exposures in Sabzevar.

Blood sampling and biochemical analysis

The assessment of fetal renal function in this study relied on key markers, with glomerular filtration rate (GFR) serving as a prominent indicator, calculated based on the serum levels of cystatin C or creatinine (Cr) [24, 46]. Routine markers such as blood urea nitrogen (BUN) and Cr were also used to evaluate kidney health status [3, 39].

Four mL of umbilical cord blood were collected from the umbilical vein immediately after delivery. The samples were transferred into serum-separating tubes containing a clot activator and left to clot at room temperature for 30 min. Following this, serum extraction was carried out through centrifugation at 3000 rpm for 15 min. The obtained serum samples were then stored at −80 ˚C until the analysis. The levels of Cr (mg/dL) and BUN (mg/dL) were analyzed using a cutting-edge auto-biochemical analyzer (Biotecnica, BT 1500, Rome, Italy) with the use of commercially supplied kits (Pars Azmoon, Tehran, Iran). The estimation of GFR (eGFR) (mL/min/1.73 m^2) was accomplished through the application of the Schwartz formula [43], as expressed by the equation:

$$\mathrm{eGFR} = k \times \mathrm{BL(cm)}/\mathrm{Cr}\left(\mathrm{mg/dL}\right), \tag{1}$$

where k represents the constant 0.45 for neonates with normal gestational age at birth, and BL is the birth length in cm. This meticulous approach to blood sampling and subsequent biochemical analysis aimed to provide a comprehensive understanding of fetal renal function, leveraging established markers in the field of nephrology.

Statistical analysis

Main analysis

To evaluate the association between exposure to PM-bound PAHs during pregnancy and fetal renal function, separate multivariable regression models were utilized. Each model analyzed PM-bound PAHs exposure individually, with umbilical renal enzymes as the dependent variable. The analysis controlled for potential confounding variables, including pre-pregnancy BMI (kg/m^2, continuous), maternal age (year, continuous), passive tobacco exposure at home during pregnancy (yes/no), parity (N, continuous), age of gestation at delivery (weeks, continuous), family income (30 ≤ million Rials/ ≥ 30 million Rials), parental education (academic degree/ high school/ elementary), and neighborhood SES indicators (unemployed percent per census tract (continuous), and illiterate percent per census tract (continuous)). Regression coefficients were reported for a one ng/m^3 increase in PAHs exposure. STATA v.16 was used for statistical analysis, and all models were thoroughly evaluated to ensure adherence to the assumptions of multiple linear regression, including linearity, absence of outliers, independence of errors, homoscedasticity, and normality of error distribution. To mitigate Type I errors and address potential issues associated with multiple comparisons, p-values were corrected using the Bonferroni correction test. This comprehensive analytical approach aimed to provide robust insights into the potential associations between PM-bound PAHs exposure during pregnancy and umbilical renal enzyme levels while carefully accounting for

relevant confounding variables. A significant level of 0.05 was applied for statistical analyses.

Quantile g-computation analysis

To comprehensively assess the combined impact of the 15 PAHs on renal function biomarkers, we utilized quantile g-computation (g-comp). This innovative approach examines the overall outcome when all exposures are simultaneously increased, regardless of whether their association with the outcome is uniform. In our study, PAH concentrations were categorized into quartiles, and a linear model was applied to determine the overall effect. This effect represented the change in the outcome when all PAHs were increased by one quartile. In the g-comp analysis, each PAH was assigned a weight value to assess its individual influence on the outcome, considering the direction of its impact. Positive or negative weight values were assigned based on the observed effects of the PAHs on the outcome. Specifically, positive weights indicate a positive association between the PAH and the outcome, suggesting an increase in the outcome with higher PAH exposure. Conversely, negative weights indicate a negative association, suggesting a decrease in the outcome with higher PAH exposure. Importantly, the sum of the weight values consistently equalled either 1 or −1, ensuring the interpretability of the results. To elaborate further, if a PAH exhibited a positive association with the outcome, it was assigned a positive weight value, indicating its contribution to increasing the outcome. Conversely, if a PAH showed a negative association with the outcome, it was assigned a negative weight value, signifying its role in decreasing the outcome. This nuanced approach allowed us to discern the differential effects of individual PAHs on renal function biomarkers within the context of simultaneous exposure to multiple compounds [45]. The models employed in this methodology were meticulously adjusted for the covariates that were also considered in the multivariable regression models. This rigorous approach allowed for a nuanced understanding of how the simultaneous increase in PAHs, each contributing differently, collectively affected renal function biomarkers.

Results

Participant characteristics: a comprehensive overview

Table 1 summarizes the demographic characteristics of the study participants, including maternal and paternal education levels, maternal age and BMI before pregnancy, maternal education levels, employment and literacy rates per census tract, passive tobacco smoking at home during pregnancy, distribution of sexes among newborns, parity, and income levels. Key findings include mean ± SD values of 16.2 ± 4.5 mg/dL for BUN, 0.79 ± 0.10 mg/dL for Cr, and 29.2 ± 4.1 mL/min/1.73 m^2 for eGFR. Paternal education levels varied, with 18% having an academic degree, 40% completing high school, and 42% having an elementary education. Maternal education levels also varied, with 25.7% holding an academic degree, 44.6% completing high school, and 29.7% having an elementary education.

Table 1 Descriptive statistics detailing the sociodemographic characteristics of participants and fetal renal function indices

Variables	Description
Umbilical renal function indices; mean ± SD	
BUN (mg/dL)	16.2 (4.5)
Cr (mg/dL)	0.79 (0.10)
eGFR (mL/min/1.73 m2)	29.2 (4.1)
Paternal education	
Academic degree; *N* (%)	81 (18%)
High school; *N* (%)	180 (40%)
Elementary; *N* (%)	189 (42%)
Maternal age (year); median (IQR)	27 (8)
Maternal BMI before pregnancy (kg/m^2); Median (IQR)	23.9 (5.8)
Maternal education	
Academic degree; *N* (%)	114 (25.7%)
High school; *N* (%)	198 (44.6%)
Elementary; *N* (%)	139 (29.7%)
Unemployed percent per census tract (%); Median (IQR)	6.9 (4.9)
Illiterate percent per census tract (%); median (IQR)	24.9 (12.9)
Passive tobacco smoking at home during pregnancy	
No; *N* (%)	360 (81.1%)
Yes; *N* (%)	84 (18.9%)
Baby sex	
Girl; N (%)	225 (50)
Boy; N (%)	225 (50)
Parity (N); median (IQR)	2 (1)
Income	
30 ≤ million Rials; *N* (%)	105 (23.3%)
≥ 30 million Rials; *N* (%)	345 (76.7%)

BUN: blood urea nitrogen; Cr: creatinine; eGFR: Estimated glomerular filtration rate; IQR: interquartile range; SD: standard deviation

The descriptive statistics of estimated PAHs compounds at residential addresses are detailed in Table 2. Specifically, for 3, 4, 5 and 6-ring PAHs, the median (interquartile range (IQR)) concentration was recorded at 2.81 (0.63), 1.22 (0.35), 1.13 (0.13) and 0.41 (0.09) ng/m^3, respectively. Lastly, the mean (SD) concentration for total PAHs was determined to be 6.24 (1.02) ng/m^3. The highest mean concentration among the PAHs compounds is observed for benzo[a]pyrene (0.50 ng/m^3) and fluorene (0.60 ng/m^3). Conversely, the lowest mean concentration is observed for anthracene and pyrene with a mean concentration of 0.17 and 0.33 ng/m^3, respectively (Table 2).

Table 2 Descriptive statistics of estimated PM-bound PAHs concentrations (ng/m^3) at residential address

PAHs compounds	Min	Mean	Max	SD	Median	IQR
3-ring PAHs	2.31	2.87	3.83	0.41	2.81	0.63
4-ring PAHs	0.83	1.22	2.14	0.26	1.22	0.35
5-ring PAHs	0.98	1.14	1.98	0.14	1.13	0.13
6-ring PAHs	0.31	0.43	0.68	0.08	0.41	0.09
Total HMW	1.41	1.66	1.99	0.12	1.65	0.18
Total LMW	1.54	3.15	5.23	0.90	3.09	1.48
Total PAHs	4.15	6.24	8.13	1.02	6.18	1.80
Benzo[g,h,i]perylene	0.12	0.27	0.95	0.12	0.24	0.09
Dibenzo[a,h]anthrancene	0.17	0.20	0.27	0.02	0.20	0.04
Indeno[1,2,3-cd]pyrene	0.18	0.24	0.35	0.05	0.23	0.07
Benzo[a]pyrene	0.37	0.50	0.75	0.09	0.46	0.09
Benzo[b]fluoranthene	0.31	0.39	0.59	0.05	0.38	0.06
Chrysene	0.29	0.38	0.47	0.04	0.37	0.05
Benzo[a]anthracene	0.21	0.26	0.35	0.03	0.26	0.03
Pyrene	0.11	0.33	0.67	0.11	0.32	0.13
Fluoranthene	0.12	0.27	0.80	0.13	0.26	0.11
Anthracene	0.00	0.17	0.40	0.09	0.20	0.14
Phenanthrene	0.31	0.42	0.65	0.08	0.41	0.12
Fluorene	0.45	0.60	0.93	0.10	0.58	0.12
Acenaphthene	0.77	1.29	1.95	0.26	1.28	0.36
Acenaphthylene	0.10	0.38	1.07	0.20	0.34	0.20
Naphthalene	0.06	0.44	1.41	0.29	0.35	0.41

IQR: interquartile range; SD: standard deviation; PAHs: polycyclic aromatic hydrocarbons

Main analysis: unraveling associations between PAH exposure and umbilical renal function

Tables 3, 4, and 5 present the outcomes of the comprehensive main analysis, scrutinizing the intricate relationships between maternal exposure to PM-bound PAHs and fetal renal function, i.e., BUN, Cr and eGFR.

Statistically significant associations at a significance level of p-value less than 0.05 emerged, indicating that increased levels of several PAH species were linked to elevated umbilical BUN concentrations. In the fully adjusted model, for every 1 ng/m^3 increase in total 6-ring PAHs, there was a notable increase in umbilical BUN by 6.97 U/L (95% CI 1.48, 12.45, $p=0.01$). Moreover, pyrene was associated with higher umbilical levels of BUN ($\beta=4.79$, 95% CI 0.73, 8.85, $p=0.02$). Furthermore, higher levels of most of the other PAHs compounds were positively associated with higher umbilical levels of BUN, while these associations were not statistically significant at a significance level of p-value less than 0.05 (Table 3).

In fully adjusted models, higher levels of 4-ring PAHs ($\beta=0.04$, 95% CI 0.02, 0.07, $p<0.01$), 6-ring PAHs ($\beta=0.30$, 95% CI 0.17, 0.42, $p<0.01$), total HMW ($\beta=0.11$, 95% CI 0.03, 0.19, $p=0.01$), total PAHs ($\beta=0.03$, 95% CI 0.02, 0.04, $p<0.01$), benzo[g,h,i]perylene ($\beta=0.10$, 95% CI 0.01, 0.18, $p=0.03$), indeno[1,2,3-cd]pyrene ($\beta=0.44$, 95% CI 0.22, 0.66, $p<0.01$), pyrene ($\beta=0.09$, 95% CI 0.00, 0.19, $p=0.05$), fluoranthene ($\beta=0.08$, 95% CI 0.01, 0.16, $p=0.04$), phenanthrene ($\beta=0.18$, 95% CI 0.05, 0.31, $p=0.01$), fluorene ($\beta=0.12$, 95% CI 0.01, 0.22, $p=0.03$), acenaphthene ($\beta=0.07$, 95% CI 0.03, 0.10, $p=0.01$), and naphthalene ($\beta=0.05$, 95%CI 0.01, 0.08, $p=0.01$) were associated with increased umbilical Cr levels. However, exposure to other PAHs did not show statistically significant associations at a significance level of p-value less than 0.05 (Table 4).

In a fully adjusted model, a rise of 1 ng/m^3 in the exposure to 3-ring PAHs, 6-ring PAHs, total HMW, total PAHs, benzo[g,h,i]perylene, indeno[1,2,3-cd]pyrene, fluoranthene, phenanthrene, fluorene, acenaphthene, acenaphthylene, and naphthalene was associated with decreases in eGFR of cord blood samples by −1.42 (95% CI −2.39, −0.46, $p<0.01$), −10.33 (95 %CI −15.10, −5.55, $p<0.01$), −3.55 (95% CI −6.72, −0.38, $p=0.03$), −1.19 (95% CI −1.56, −0.82, $p<0.01$), −4.38 (95% CI −7.72, −1.05, $p=0.01$), −14.67 (95% CI −23.23, −6.11, $p<0.01$), −3.31 (95% CI −6.40, −0.22, $p=0.04$), −6.24 (95% CI −11.22, −1.26, $p=0.01$), −4.59 (95% CI −8.49, −0.68, $p=0.02$), −2.25 (95% CI −3.76, −0.74, $p<0.01$), −2.18 (95% CI −4.12, −0.25, $p=0.03$), and −1.71 (95% CI −3.04, −0.38, $p=0.01$), respectively. However,

Table 3 Regression coefficients of exposure to PM-bound PAHs during pregnancy and umbilical BUN

Pollutants	Model	Regression coefficients (95% confidence interval)	*p*-value
3-ring PAHs	Crude	0.14 (−0.89, 1.17)	0.79
	Adjusted*	0.60 (−0.50, 1.70)	0.29
4-ring PAHs	Crude	−0.35 (−1.97, 1.26)	0.67
	Adjusted	0.40 (−1.34, 2.14)	0.65
5-ring PAHs	Crude	3.10 (0.08, 6.12)	**0.04**
	Adjusted	2.60 (−0.66, 5.87)	0.12
6-ring PAHs	Crude	6.16 (0.95, 11.36)	**0.02**
	Adjusted	6.97 (1.48, 12.45)	**0.01**
Total HMW	Crude	2.17 (−1.25, 5.60)	0.21
	Adjusted	1.88 (−1.73, 5.49)	0.31
Total LMW	Crude	−0.37 (−0.83, 0.09)	0.12
	Adjusted	−0.17 (−0.67, 0.32)	0.49
Total PAHs	Crude	0.47 (0.06, 0.88)	**0.02**
	Adjusted	0.33 (−0.11, 0.76)	0.15
Benzo[g,h,i]perylene	Crude	5.03 (1.62, 8.44)	**< 0.01**
	Adjusted	2.56 (−1.24, 6.36)	0.19
Dibenzo[a,h]anthrancene	Crude	6.37 (−11.12, 23.86)	0.47
	Adjusted	4.92 (−13.65, 23.49)	0.60
Indeno[1,2,3−cd]pyrene	Crude	−0.07 (−9.15, 9.02)	0.99
	Adjusted	5.05 (−4.77, 14.88)	0.31
Benzo[a]pyrene	Crude	1.19 (−3.71, 6.09)	0.63
	Adjusted	−0.59 (−5.70,4.53)	0.82
Benzo[b]fluoranthene	Crude	2.35 (−6.39, 11.09)	0.60
	Adjusted	−0.17 (−9.31, 8.96)	0.97
Chrysene	Crude	6.92 (−3.83, 17.67)	0.21
	Adjusted	6.48 (−4.90, 17.86)	0.26
Benzo[a]anthracene	Crude	−9.61 (−23.39, 4.17)	0.17
	Adjusted	−1.41 (−16.37, 13.55)	0.85
Pyrene	Crude	3.50 (−0.38, 7.38)	0.08
	Adjusted	4.79 (0.73, 8.85)	**0.02**
Fluoranthene	Crude	1.04 (−2.30, 4.38)	0.54
	Adjusted	1.50 (−2.02, 5.01)	0.40
Anthracene	Crude	−7.30 (−11.80, −2.79)	**< 0.01**
	Adjusted	−6.46 (−11.23, −1.69)	**0.01**
Phenanthrene	Crude	2.35 (−2.96, 7.66)	0.38
	Adjusted	4.71 (−0.95, 10.38)	0.10
Fluorene	Crude	−1.02 (−5.17, 3.13)	0.63
	Adjusted	1.02 (−3.43, 5.47)	0.65
Acenaphthene	Crude	0.37 (−1.23, 1.98)	0.65
	Adjusted	0.56 (−1.17, 2.29)	0.53
Acenaphthylene	Crude	0.64 (−1.45, 2.73)	0.55
	Adjusted	0.20 (−2.01, 2.40)	0.86
Naphthalene	Crude	1.24 (−0.19, 2.67)	0.09
	Adjusted	1.06 (−0.46, 2.57)	0.17

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; PAHs: polycyclic aromatic hydrocarbons

* Models were adjusted for pre-pregnancy BMI, maternal age, passive tobacco exposure at home during pregnancy, parity, age of gestation at delivery, family income, parental education, and neighborhood SES indicators

Blued items are statistically significant

associations with exposure to other PAHs were not statistically significant at a significance level of p-value less than 0.05 (Table 5).

Mixture exposure to PM-bound PAHs

The thorough quantile g-computation analysis provided further insight into the collective impact of the PAHs mixture on fetal renal function indicators. Positive correlations were observed, suggesting that with each one-quartile escalation in the PAHs mixture, umbilical BUN and Cr levels increased. Specifically, a quartile rise in the PAHs mixture corresponded to a 1.08 mg/dL (95% CI 0.04, 2.11, $p=0.04$) and a 0.02 mg/dL (95% CI −0.00, 0.05, $p=0.05$) elevation in BUN and Cr, respectively. Additionally, exposure to the PAHs mixture was linked to a reduction in eGFR. With each one-quartile increment in the PAHs mixture, there was a −1.09 mL/min/1.73 m2 (95% CI −2.03, −0.14, $p=0.02$) decline in eGFR (Table 6).

Figure 1 presents a graphical depiction illustrating the significance of PAHs in their combined impact on BUN, Cr, and eGFR through quantile g-computation, providing a more detailed understanding of how each individual PAH species contributes to renal function outcomes.

Discussion

To our knowledge, this study marks the pioneering investigation into the correlation between maternal exposure to PAHs and fetal renal function. Our findings reveal heightened umbilical BUN and Cr levels in association with increased exposure to PM-bound PAHs. Additionally, exposure to PAHs mixture was related with lower eGFR.

Comparing with available evidence

In our study, we observed a median ambient total concentration of PAHs at 6.2 (IQR: 1.8) ng/m^3. These findings closely correspond to results reported in previous studies conducted both within Iran and internationally. For instance, Kosari et al. [27] conducted research in Sabzevar, Iran, which unveiled a median PM-bound PAHs concentration of 5.87 (IQR: 4.72) ng/m^3 [27]. Similarly, a study by Ali-Taleshi et al. [4] in Tehran, recognized as one of Iran's most polluted cities, reported an annual mean concentration of total PM-bound PAHs at 30.1 ng/m^3 [4]. Shams Solari et al. [44], also in Tehran, Iran, found that the average concentration of ΣPAHs ranged from 5.54 ng/m^3 in remote suburban areas to 20.67 ng/m^3 in heavily trafficked roadside sites [44]. Furthermore, Wang et al. [53] conducted a study in Vladivostok, Russia, which revealed distinct seasonal variations, with mean (SD) ΣPAHs concentrations

Table 4 Regression coefficients of exposure to PM-bound PAHs during pregnancy and umbilical Cr

Pollutants	Model	Regression coefficients (95% condolence interval)	*p*-value
3-ring PAHs	Crude	0.04 (0.01, 0.06)	**< 0.01**
	Adjusted	0.04 (0.02, 0.07)	**< 0.01**
4-ring PAHs	Crude	0.03 (−0.01, 0.06)	0.17
	Adjusted	0.04 (0.00, 0.08)	**0.04**
5-ring PAHs	Crude	0.01 (−0.07, 0.08)	0.87
	Adjusted	0.03 (−0.05, 0.10)	0.52
6-ring PAHs	Crude	0.24 (0.12, 0.36)	**< 0.01**
	Adjusted	0.30 (0.17, 0.42)	**< 0.01**
Total HMW	Crude	0.09 (0.01, 0.17)	**0.02**
	Adjusted	0.11 (0.03, 0.19)	**0.01**
Total LMW	Crude	0.01 (0.00, 0.02)	0.25
	Adjusted	0.01 (0.00, 0.02)	0.11
Total PAHs	Crude	0.03 (0.02, 0.04)	**< 0.01**
	Adjusted	0.03 (0.02, 0.04)	**< 0.01**
Benzo[g,h,i]perylene	Crude	0.11 (0.03, 0.18)	**0.01**
	Adjusted	0.10 (0.01, 0.18)	**0.03**
Dibenzo[a,h]anthrancene	Crude	−0.02 (−0.43, 0.39)	0.93
	Adjusted	−0.25 (−0.68, 0.18)	0.26
Indeno[1,2,3− cd]pyrene	Crude	0.32 (0.11, 0.53)	**< 0.01**
	Adjusted	0.44 (0.22, 0.66)	**< 0.01**
Benzo[a]pyrene	Crude	0.01 (−0.10, 0.12)	0.86
	Adjusted	0.05 (−0.07, 0.16)	0.44
Benzo[b]fluoranthene	Crude	0.01 (−0.19, 0.22)	0.90
	Adjusted	0.08 (−0.12, 0.29)	0.43
Chrysene	Crude	0.06 (−0.19, 0.31)	0.63
	Adjusted	0.13 (−0.13, 0.39)	0.33
Benzo[a]anthracene	Crude	0.19 (−0.13, 0.51)	0.25
	Adjusted	0.29 (−0.05, 0.63)	0.09
Pyrene	Crude	0.11 (0.02, 0.20)	**0.02**
	Adjusted	0.09 (0.00, 0.19)	**0.05**
Fluoranthene	Crude	0.08 (0.01, 0.16)	**0.04**
	Adjusted	0.08 (0.01, 0.16)	**0.04**
Anthracene	Crude	−0.12 (−0.22, −0.01)	**0.03**
	Adjusted	−0.10 (−0.21, 0.01)	0.08
Phenanthrene	Crude	0.13 (0.01, 0.25)	**0.04**
	Adjusted	0.18 (0.05, 0.31)	**0.01**
Fluorene	Crude	0.10 (0.00, 0.20)	**0.04**
	Adjusted	0.12 (0.01, 0.22)	**0.03**
Acenaphthene	Crude	0.06 (0.02, 0.09)	**0.01**
	Adjusted	0.07 (0.03, 0.10)	**0.01**
Acenaphthylene	Crude	0.05 (0.00, 0.10)	**0.04**
	Adjusted	0.04 (−0.01, 0.09)	0.10
Naphthalene	Crude	0.06 (0.03, 0.09)	**< 0.01**
	Adjusted	0.05 (0.01, 0.08)	**0.01**

Note: PAHs: polycyclic aromatic hydrocarbons; Cr: creatinine

* Models were adjusted for pre-pregnancy BMI, maternal age, passive tobacco exposure at home during pregnancy, parity, age of gestation at delivery, family income, parental education, and neighborhood SES indicators

Blued items are statistically significant

recorded at 18.6 ± 9.80 ng/m^3 in winter and 0.54 ± 0.21 ng/m^3 in summer [53].

Our study pioneers the investigation of the relationship between PAHs exposure and renal function in newborns, presenting novel insights into a previously unexplored domain. While direct comparative analyses with prior studies on this specific topic are lacking, our findings align with existing literature examining the broader relationship between air pollution as well as PAHs compounds and renal function across diverse populations. A study by Rahmani Sani et al. [39] on 150 mother pairs in Sabzevar, Iran, reported that a significant inverse correlation was identified between exposure to PM_1, $PM_{2.5}$, PM_{10}, and the total street length within a 100-m radius around residential areas (an indicator of exposure to traffic) and eGFR levels. Additionally, a notable positive correlation was observed between exposure to PM and street length within a 100-m buffer and serum levels of Cr. However, they did not find any statistically significant associations with BUN [39]. A systematic review and meta-analysis conducted by Wu et al. in 2020 unveiled consistent trends linking exposure to PM2.5 and PM10 with a decrease in estimated glomerular filtration rate (eGFR) [55]. Another study by Sun et al. in 2021, which involved 30,442 adults, demonstrated a significant positive correlation between various PAHs compounds and the risk of kidney stones, even after adjusting for potential confounders. Individuals with higher exposure to total PAHs, 2-hydroxynaphthalene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, and 9-hydroxyfluorene exhibited a heightened likelihood of developing kidney stones compared to those with lower exposure levels [48]. Rahman et al. [38] in a study on US adult population reported a significant correlation between chronic kidney disease (CKD) and the presence of urinary 2-hydroxynaphthalene, a type of PAHs biomarker [38]. Another study by Farzan et al. [16] on 660 adolescents aged 12–19 reported that the presence of urinary PAH metabolites showed associations with serum uric acid, GGT, and CRP levels, indicating potential effects on cardiometabolic and kidney function among adolescents [16]. Yuan et al. [58] reported that living in closer proximity to areas with higher arsenic and PAH exposure was linked to an increased risk of renal impairment and CKD among 2069 adult residents residing near petrochemical industries in Taiwan [58].

Potential mechanisms

Exposure to PAHs during pregnancy may impact fetal renal function through various biological mechanisms. Firstly, PAHs can traverse the placental barrier, entering the fetal circulation and directly influencing renal tissues, potentially disrupting normal renal development [7,

Table 5 Regression coefficients of exposure to PM-bound PAHs during pregnancy and eGFR

Pollutants	Model	Regression coefficients (95% confidence interval)	*p*-value
3-ring PAHs	Crude	−1.21 (−2.14, −0.29)	**0.01**
	Adjusted	−1.42 (−2.39, −0.46)	**< 0.01**
4-ring PAHs	Crude	−1.08 (−2.54, 0.38)	0.15
	Adjusted	−1.39 (−2.92, 0.14)	0.08
5-ring PAHs	Crude	−0.06 (−2.80, 2.68)	0.97
	Adjusted	−0.95 (−3.84, 1.94)	0.52
6-ring PAHs	Crude	−8.08 (−12.76, −3.41)	**< 0.01**
	Adjusted	−10.33 (−15.10, −5.55)	**< 0.01**
Total HMW	Crude	−3.38(−6.47, −0.30)	**0.03**
	Adjusted	−3.55 (−6.72, −0.38)	**0.03**
Total LMW	Crude	−0.20 (−0.62, 0.22)	0.35
	Adjusted	−0.29 (−0.72, 0.15)	0.20
Total PAHs	Crude	−1.19 (−1.55, −0.84)	**< 0.01**
	Adjusted	−1.19 (−1.56, −0.82)	**< 0.01**
Benzo[g,h,i]perylene	Crude	−4.59 (−7.67, −1.50)	**< 0.01**
	Adjusted	−4.38 (−7.72, −1.05)	**0.01**
Dibenzo[a,h]anthrancene	Crude	1.66 (−14.15, 17.48)	0.84
	Adjusted	8.23 (−8.15, 24.60)	0.32
Indeno[1,2,3−cd]pyrene	Crude	−10.68 (−18.83, −2.53)	**0.01**
	Adjusted	−14.67 (−23.23, −6.11)	**< 0.01**
Benzo[a]pyrene	Crude	0.28 (−4.14, 4.71)	0.90
	Adjusted	−0.47 (−4.98, 4.05)	0.84
Benzo[b]fluoranthene	Crude	−0.66 (−8.57, 7.24)	0.87
	Adjusted	−2.27 (−10.32, 5.79)	0.58
Chrysene	Crude	−0.05 (−9.78, 9.68)	0.99
	Adjusted	−1.16 (−11.21, 8.90)	0.82
Benzo[a]anthracene	Crude	−8.69 (−21.14, 3.77)	0.17
	Adjusted	−11.72 (−24.87, 1.43)	0.08
Pyrene	Crude	−3.90 (−7.40, −0.40)	**0.03**
	Adjusted	−3.39 (−6.98, 0.20)	0.06
Fluoranthene	Crude	−3.44 (−6.45, −0.44)	**0.02**
	Adjusted	−3.31 (−6.40, −0.22)	**0.04**
Anthracene	Crude	3.07 (−1.04, 7.17)	0.14
	Adjusted	2.34 (−1.90, 6.58)	0.28
Phenanthrene	Crude	−5.04 (−9.82, −0.26)	**0.04**
	Adjusted	−6.24 (−11.22, −1.26)	**0.01**
Fluorene	Crude	−4.30 (−8.03, −0.57)	**0.02**
	Adjusted	−4.59 (−8.49, −0.68)	**0.02**
Acenaphthene	Crude	−1.74 (−3.18, −0.30)	**0.02**
	Adjusted	−2.25 (−3.76, −0.74)	**0.00**
Acenaphthylene	Crude	−2.41 (−4.29, −0.53)	**0.01**
	Adjusted	−2.18 (−4.12, −0.25)	**0.03**
Naphthalene	Crude	−2.04 (−3.33, −0.76)	**< 0.01**
	Adjusted	−1.71 (−3.04, −0.38)	**0.01**

PAHs: polycyclic aromatic hydrocarbons; eGFR: estimated glomerular filtration rate

* Models were adjusted for pre-pregnancy BMI, maternal age, passive tobacco exposure at home during pregnancy, parity, age of gestation at delivery, family income, parental education, and neighborhood SES indicators

Blued items are statistically significant

Table 6 The quantile g-computation estimates the overall effects of 15 PAHs on fetal renal function indices

Renal function indicator	Estimate (95% CI)	*p*-value
BUN	1.08 (0.04, 2.11)	0.04
Cr	0.02 (−0.00, 0.05)	0.05
eGFR	−1.09 (−2.03, −0.14)	0.02

BUN: blood urea nitrogen; Cr: creatinine; eGFR: estimated glomerular filtration rate;

* Models were adjusted for pre-pregnancy BMI, maternal age, passive tobacco exposure at home during pregnancy, parity, age of gestation at delivery, family income, parental education, and neighborhood SES indicators

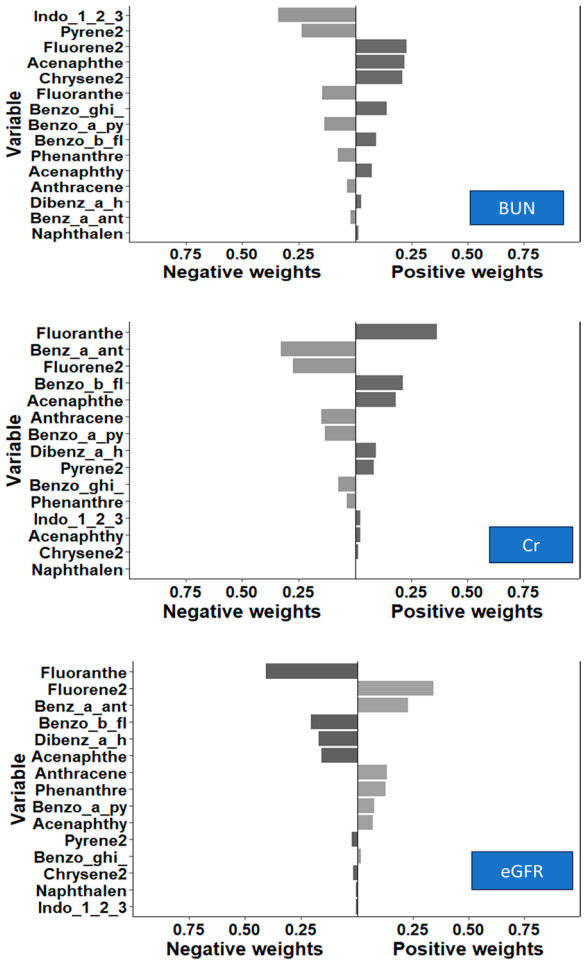

Fig. 1 Weight of PAHs in joint effect on BUN, Cr and eGFR in quantile g-computation. (Positive or negative weights indicate the contribution of positive or negative partial effects to the overall effect for each PAH. The length of the bars corresponds to the magnitude of these weights.)

36]. Secondly, PAH exposure is known to induce oxidative stress, leading to cellular damage and dysfunction in the developing fetal kidneys [22, 34]. This oxidative stress may arise from the generation of reactive oxygen species

triggered by PAH exposure [30, 34]. Additionally, PAHs have been associated with inflammatory responses, and maternal exposure could incite inflammation in the fetal kidneys, contributing to abnormalities in renal development [5, 18]. Furthermore, the endocrine-disrupting effects of PAHs may interfere with hormonal regulation during fetal development, particularly within the renin–angiotensin system, potentially resulting in altered renal function [11, 19, 20]. Epigenetic changes, such as modifications in DNA methylation, histone structure, or microRNA expression patterns, could be induced by PAH exposure, influencing gene expression in fetal kidneys and leading to persistent alterations in renal function. PAH exposure might also impact renal blood vessels, compromising vascular development and thereby affecting blood flow and nutrient supply to the developing kidneys [10, 13, 15]. Moreover, PAH exposure could impair nephrogenesis, disrupting the formation and differentiation of nephrons, the functional units of the kidney [42, 51]. Finally, the formation of toxic metabolites during PAH metabolism may directly damage renal cells or interfere with normal cellular processes, contributing to changes in fetal renal function [8, 12]. These interconnected mechanisms underscore the complex ways in which PAH exposure during pregnancy may adversely affect fetal renal health.

Limitations

This study has several limitations that warrant consideration in future research. Firstly, establishing a causal link between exposure and outcomes is challenging in cross-sectional studies like ours, emphasizing the need for longitudinal investigations. Secondly, the use of renal enzymes as indicators of renal function. The most appropriate method for assessing fetal renal function involves prenatal imaging studies, particularly renal ultrasound. Renal ultrasound allows for the visualization of fetal kidneys, ureters, and bladder, enabling the detection of structural abnormalities and anomalies. Additionally, assessment of amniotic fluid volume and composition can provide indirect insights into fetal urine production and renal function [14, 31]. Furthermore, our evaluation of ambient PAHs exposure primarily relied on outdoor concentrations, overlooking the considerable amount of time pregnant women spend indoors. This methodology may not accurately capture the true level of in utero exposure. Additionally, our utilization of a model to estimate maternal exposure during pregnancy introduces variability compared to personalized monitoring approaches. We exclusively examined exposure to PAHs throughout the entire pregnancy; however, we did not assess exposure during different windows of exposure, such as each trimester. We focused on examining the effects of individual PAH exposures separately, disregarding the common scenario of concurrent exposure to multiple PAHs in the human body, potentially leading to synergistic effects. Although total PAH levels served as a proxy for exposure to multiple PAHs, our study did not investigate dietary sources of PAH exposure, which represent a significant contributor to overall PAH exposure.

Conclusion

Noteworthy correlations emerged, suggesting a link between increased levels of various PAHs species and raised umbilical levels of BUN and Cr, implying possible renal dysfunction. Notably, exposure to certain PAHs compounds demonstrated statistically significant associations with umbilical BUN, Cr, and eGFR levels, highlighting the potential impact of PAH exposure on fetal renal function. Positive associations were observed, indicating that increases in the PAHs mixture were related with higher BUN and Cr, as well as lower eGFR. The findings of this study underscore the importance of considering environmental exposures, such as PAHs, in assessing renal health outcomes among neonates. Further research, particularly prospective studies, is warranted to better understand the long-term health implications of PAH exposure during pregnancy and its potential impact on renal function later in life.

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Author contributions

All authors participated in the study design. Ch.Y.H. authored the initial manuscript draft. C.L. and N.S.M. conducted sample analysis and manuscript revisions. Sh.A.H and A.K. performed statistical analyses and contributed to manuscript revisions. J.S.M, A.P., N.J., and S.H.J.A. reviewed the manuscript. M.L.N. oversaw the study design, data analyses, and manuscript revisions. The paper and Supplementary Information underwent review and approval by all authors.

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Data availability

The data will be available on request from the corresponding author.

Declarations

Ethical approval and consent to participate

The Ethics Committee of Sabzevar University of Medical Sciences, Sabzevar, Iran, approved this study (IR.MEDSAB.REC.1395.82). Before enrollment, all participants provided their signature on the consent form approved by the Ethics Committee of Sabzevar University of Medical Sciences, Sabzevar, Iran.

Consent for publication
Not applicable.

Competing interests
The authors disclose that they have no competing interests.

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