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Associations of polycyclic aromatic hydrocarbons exposure with perinatal anxiety symptoms

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Abstract

Background Polycyclic aromatic hydrocarbons (PAHs) have recently garnered attention for their possible neurotoxic effects. This study was meticulously crafted to assess the influence of PAHs exposure on the emergence of perinatal anxiety symptoms.

Methods From April 28, 2020, to July 20, 2021, a case–control study recruiting eligible pregnant women was conducted in two primary hospitals in Hefei City, China. Professionals employed the 7-item Generalized Anxiety Disorder Scale to assess the participants' anxiety symptoms during pregnancy and postpartum via WeChat. Urinary concentrations of 12 hydroxylated PAH metabolites during pregnancy and postpartum were quantified through gas chromatography-tandem triple quadrupole mass spectrometry. Logistic regression analysis and mixed exposure modeling (BKMR model) were employed in our study to probe into the associations between PAHs exposure and perinatal anxiety symptoms.

Results Our study incorporated 642 participants (279 cases and 363 controls). Multivariable logistic regression models revealed significant dose–response relationships between the levels of individual PAH metabolites in urine and prenatal anxiety symptoms. Compared to pregnant women in the lowest exposure tertile, those in the highest tertiles of urinary concentrations of 2-OHNA, 9-OHFLU, ∑OHFLU, 2-OHDBF, and ∑OH-PAHs had increased risk of experiencing prenatal anxiety (OR = 1.915, 95%CI: 1.271–2.886; OR = 2.084, 95%CI: 1.358–3.199; OR = 2.055, 95%CI: 1.355–3.117; OR = 1.675, 95%CI: 1.119–2.507; OR = 1.870, 95%CI: 1.228–2.847, respectively). BKMR analysis indicated a significant trend of increasing likelihood of prenatal anxiety symptoms with higher levels of the OH-PAHs mixture. Meanwhile, follow-up of 230 pregnant women until 42 days postpartum revealed that increased prenatal urinary concentrations of 2-OHFLU and ∑OHFLU were associated with a higher risk of postpartum anxiety symptoms (OR = 2.101, 95%CI: 1.000–4.414 for the medium vs. low 2-OHFLU exposure; OR = 2.277, 95%CI: 1.080–4.799 for the high vs. low ∑OHFLU exposure, respectively).

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Conclusions Our study brings to light a potentially strong positive link between PAHs exposure and perinatal anxiety symptoms.

Keywords Polycyclic aromatic hydrocarbons, Perinatal anxiety symptoms, Prenatal anxiety symptoms, Case–control study

Introduction

Polycyclic aromatic hydrocarbons (PAHs), characterized by two or more benzene rings, represent a class of widespread environmental contaminants with significant public health implications [2, 23]. For non-smoking individuals, the predominant source of PAH exposure is through dietary intake [31]. Following absorption, these compounds undergo hepatic biotransformation, ultimately being excreted as hydroxylated metabolites (OH-PAHs) through urinary and fecal routes [1, 22]. The toxicological profile of PAHs has been extensively documented, with particular concern regarding their transgenerational effects mediated through maternal metabolic disruption and epigenetic modifications in placental DNA [20, 21].

The topic of environmental pollution and mental health has received much attention in recent years. A comprehensive meta-analysis of 23 longitudinal cohorts revealed significant associations between nitrogen dioxide (NO_2) and particulate matter ($PM_{2.5}$) exposure and elevated depression symptoms risk [3]. Parallel findings from a multicenter pregnancy cohort ($n=10{,}209$) demonstrated that gestational exposure to SO_2, PM_{10}, CO, and NO_2 increased postpartum depression symptoms susceptibility by 42 days [9]. Perera et al. examined children aged 6–7 years ($n=253$) and discovered that the level of prenatal exposure to PAHs was positively linked with the likelihood of anxiety symptoms in children [19]. As a complex physiological state, pregnancy brings both physical and psychological challenges for women, which can lead to an increased likelihood of anxiety symptoms. Existing studies have documented trimester-specific prevalence rates of antenatal anxiety at 18.2% (first trimester), 19.1% (second trimester), and 24.6% (third trimester) [7]. Juarez Padilla et al. reported a 21% prevalence of prenatal anxiety symptoms during pregnancy, which decreased to 18% in the postpartum period ($n=234$) [14]. Contemporary research identifies multifactorial determinants of perinatal anxiety, encompassing: (1) neurosteroid fluctuations [10]; (2) socioeconomic disparities [16]; (3) maternal and fetal health status [5], (4)environmental toxicant exposure [3, 29]. Emerging evidence has established associations between various environmental pollutants and mental health outcomes, significant knowledge gaps remain in understanding the specific effects of PAHs on perinatal mental health. Despite PAHs being recognized as one of the most pervasive classes of environmental contaminants, there is a paucity of research examining their potential impact on perinatal anxiety symptoms. This gap is particularly notable given the unique vulnerability of pregnant women to environmental exposures and the potential for transgenerational effects. Furthermore, existing studies have largely focused on individual PAH compounds, with limited investigation into the effects of complex PAH mixtures and their potential interactions, which more accurately reflect real-world exposure scenarios.

To address this critical knowledge gap, we conducted a case–control study in Hefei, China, investigating both the internal PAH exposure burden in pregnant women and its potential association with perinatal anxiety symptoms risk. This dual focus on exposure quantification and clinical correlation provides novel insights into the neurotoxicological impacts of PAHs during vulnerable gestational periods.

Material and methods

Participant recruitment

We recruited pregnant women for a case–control study between April 28, 2020 and July 20, 2021 at two primary hospitals in Hefei City. Pregnant women attending the hospitals for prenatal checkups were recruited for the study and their anxiety symptoms were assessed utilizing the 7-item Generalized Anxiety Disorder scale (GAD-7) [11]. We categorized pregnant women into case and control groups based on GAD-7 scores. The inclusion criteria for pregnant women in this study were as follows: pregnant women aged ≥ 18 years old; able to independently complete the basic questionnaire and emotional screening scale via mobile phone; voluntarily participating in the study; and signing of an informed consent form. Pregnant women who lacked urine samples or basic information were excluded from the study. Finally, 279 cases and 363 controls ($n=642$) were enrolled. More details on the inclusion of pregnant women are given in Fig. 1. Comparative analysis of baseline characteristics, as detailed in Supplementary Table S1, revealed no statistically significant differences ($P>0.05$) between included and excluded participants across all measured demographic parameters except for pregnancy intention status ($P<0.05$), suggesting minimal selection bias in our study population. Among the 642 participants, 230 women (44

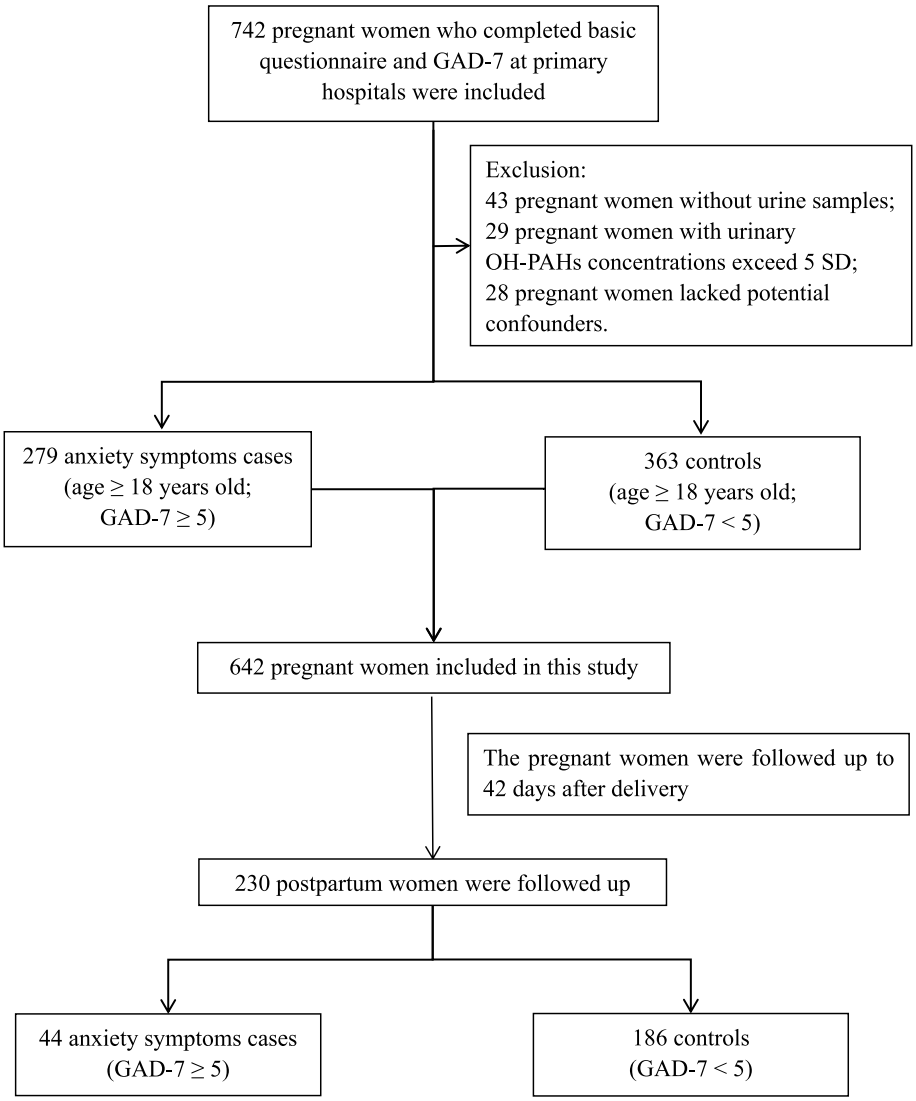

Fig. 1 Flow chart describing the inclusion of study participants. Abbreviation: SD, standard deviation

cases and 186 controls) were followed up to 42 days postpartum. Postnatal anxiety symptoms were assessed, and urine samples were collected again at 42 days postpartum. This study was conducted under the guidance of the Declaration of Helsinki, and all participants in this study signed informed consent forms. The Ethics Committee of Anhui Medical University has approved our work (No: 83220006).

Outcome measure

The online screening platform was developed using WeChat, a widely utilized social media application in China. Participants accessed the GAD-7 questionnaire by scanning a QR code under the supervision of primary healthcare providers during pregnancy (mean gestational age 20.54 ± 8.39 weeks). The GAD-7, a validated instrument with scores ranging from 0 to 21 [27], was administered once during pregnancy to assess anxiety symptoms. Consistent with previous studies in Chinese populations, we established a cut-off score of ≥ 5 for identifying significant anxiety symptoms, based on the scale's demonstrated reliability and validity in assessing anxiety symptoms among Chinese pregnant women [11]. In addition, we conducted follow-up assessments at 42 days postpartum (± 7 days) using the same instrument once again. The primary outcomes of this study were the GAD-7 scores measured during pregnancy and at 42-day postpartum follow-up.

Exposure to PAHs

Pregnant women were instructed to collect urine samples during registration, which were then packaged and stored in a −80 °C refrigerator by specialized personnel. The urine samples were transported to Anhui Medical University through the cold chain, and the level of PAH metabolites concentrations were detected at Anhui Medical University. The concentrations of 12 OH-PAHs, including 9-, 4-, 1-, 3-, 2-hydroxyphenanthrene (9-, 4-, 1-, 3-, 2-OHPHE), 2-hydroxydibenzofuran (2-OHDBF), 2-, 1-hydroxynaphthalene (2-, 1-OHNA), 9-, 2-, 3-hydroxyfluorene (9-, 2-, 3-OHFLU), and 1-hydroxypyrene (1-OHP), were determined by GC–MS/MS of Agilent. The standard chemicals were purchased from Chiron (9-OHFLU and 2-OHDBF) (Trondheim, Norway), Dr. Ehrenstorfer (9-, 4-, 1-, 3-, 2-OHPHE, 2-, and 2-OHNA) (Augsburg, Germany), Toronto Research Chemicals Inc. (2-, and 3-OHFLU) (Ontario, Canada), and Sigma–Aldrich (1-OHP) (Munich, Germany).. The internal standards were obtained from Toronto Research Chemicals Inc. {1-Hydroxynaphthalene-d7 (1-OHNA-d7) and 1-Hydroxypyrene-d9 (1-OHP-d9)} (Ontario, Canada).

To detect urinary PAH metabolites, 3.0 mL of urine was added to 20 μL of β-Glucuronidase/sulphatase (CNW Technologies GmbH, Germany), 1.0 mL of sodium acetate (pH = 5.0, 0.5 M) and 20 μL of mixtures of the internal standard solution, and then incubated at 37 ℃ for 12 h. Subsequently, we added $MgSO_4 \cdot 7H_2O$ to the urine to achieve saturation, followed by three extractions of 1.5 mL n-hexane from saturated urine. The target compounds were reconstituted with 100 μL of bistrimethylsilyl-trifluoroacetamide (Regis Technologies Inc., USA) and detected by GC–MS/MS. Each analytical batch consisted of two quality control samples (urine with either low or high concentrations of target compounds added) and one blank sample (purified water). The lab technician knew no information about the participants. The linearity of each PAH metabolite was excellent ($R^2 > 0.99$), and the recoveries ranged from 91.86% to 121.84%. The method limits of detection (LODs) in this study ranged from 0.010 to 0.074 ng/mL (Table S2). In addition, we adjusted the concentration of the OH-PAHs component in urine using urine specific gravity (SG) to account for the dilution of urine [15].

Covariates

Participants were instructed to fill in basic information through a WeChat-based electronic questionnaire. More details on the questionnaire can be seen in the supplementary material. Demographic information included age and gestational week when pregnant woman was recruited, body mass index (BMI), type of residential location ("rural" and "urban"), level of education ("college or above", "senior high school or technical secondary school" and "junior high school or below"), marital status ("married" and "other"), occupational status during pregnancy ("out of work", "full-time" and "other"), annual household income after tax (< 50 000, 50 000 ~ 99 999, 100 000 ~ 199 999 and ≥ 200 000 CNY), pregnancy intention ("unintentional pregnancy" and "intentional pregnancy"), gravidity, history of adverse pregnancy ("yes" or "no"), infertility ("yes" or "no"), history of perinatal disease ("yes" or "no") and tobacco exposure status ("yes" or "no"). We categorized both active smoking and secondhand smoke exposure as tobacco exposure. Active smoking was when participants smoked a total of more than 100 cigarettes to date, while passive smoking was when participants were exposed to secondhand smoke for at least 15 min per day.

Statistical analysis

Any concentration below LODs is expressed as LOD/$\sqrt{2}$. Due to the skewed distribution of OH-PAHs components in participants' urine, we performed a natural logarithm (Ln) transformation of the concentration of the OH-PAHs components. When the detection rate of certain OH-PAHs components in urine was less than 50%, it was excluded from the regression analysis.

We expressed continuous variables as the mean and standard deviation (SD). Meanwhile, Student's *t* test was applied to assess the differences between pregnant women in the case group and control group. Categorical variables were reported as the number of samples (n) and percentages (%) and were tested by Chi-square test. In addition, we used Spearman correlation analysis to examine the correlations among the OH-PAHs components in urine.

We employed logistic regression models to investigate the relationship between the level of individual OH-PAHs components concentrations in urine and the likelihood of prenatal anxiety symptoms. In regression models, the concentrations of OH-PAHs components in urine were analyzed as categorical variables in tertiles. To examine the nonlinear dose–response associations, the components concentrations were divided into tertiles based on the control group, and the lowest tertiles were used as reference groups. The median of each OH-PAH component tertile was used as a continuous variable in the analysis to assess the *P*-value for the linear trend of odds ratio (OR) for each OH-PAH component. We selected potential covariates based on directed acyclic graphs (DAGs) (Fig. S1).

We used the Bayesian kernel machine regression model (BKMR) to analyze the effects of combined PAH exposure on prenatal anxiety symptoms [6]. The model incorporated pairwise interaction terms among PAH

metabolites to quantify potential combined effects within the exposure mixture. We employed 10 000 iterations in the Bayesian Markov Chain Monte Carlo (MCMC) simulation to estimate the posterior distribution of model parameters and to characterize the uncertainty of mixture effects. Additionally, the model adjusted for confounding factors such as age, gestational week, level of education, pregnancy intention, history of adverse pregnancy outcomes, and tobacco exposure, enabling us to comprehensively understand the complex interactions among multiple PAH metabolites and their impact on anxiety symptoms during pregnancy. Furthermore, we computed the posterior inclusion probability (PIPs) of PAH metabolites. This was done to illustrate the contribution of each individual PAH metabolite component to the overall mixture effect [6].

Moreover, logistic regression analysis was employed to investigate the association between the concentration levels of OH-PAHs components in urine during pregnancy and the postpartum period and the probability of developing postpartum anxiety symptoms. All statistical operations were conducted in SPSS 23.0 and R 4.1.2. The significance level of this study was established at 0.05.

Results

Demographic characteristics of the pregnant women

The basic characteristics of the 642 pregnant women enrolled in this case–control study are presented in Table 1. The mean (± SD) age of the cases and controls were 28.29 (± 4.50) and 29.15 (± 3.99) years. The mean (± SD) gestational week of the case group was 18.37 (± 7.96) weeks, which was shorter than that of the control group (22.22 ± 8.21 weeks). Women in the case group had a higher level of education, a higher rate of unintentional pregnancy and adverse pregnancy history than the control pregnant women ($P < 0.05$). Moreover, no significant variations were observed in marital status, pre-pregnancy BMI, type of residential location, annual household income after tax, occupational status during pregnancy, gravidity, smoking history, infertility, tobacco exposure and perinatal disease history between the case pregnant women and the control pregnant women ($P > 0.05$). Additionally, the GAD-7 scores during pregnancy were higher than those postpartum (Table S2).

The concentrations of PAH metabolites in urine and the relationships among various components of PAH metabolites

Table S2 presents the median concentrations of prenatal and postpartum PAH metabolites. Among the prenatal samples, 2-OHNA had the highest median concentration, reaching 1.924 ng/mL after SG adjustment. 2-OHFLU followed, with a median SG-adjusted concentration of 0.680 ng/mL. In the postpartum urine, 2-OHNA again showed the highest median concentration, measured at 1.966 ng/mL (SG-adjusted).

To examine the correlations between different components of OH-PAHs in pregnant women's urine, we conducted a spearman correlation analysis (Table S3). The analysis results indicated that the strongest correlation coefficient (0.53) was observed between 1-OHPHE and 2-OHPHE. Subsequently, correlations of 0.46 were found between 3-OHFLU and 4-OHPHE, as well as between 3-OHFLU and 9-OHPHE. In contrast, the weakest correlation ($r = 0.00$) was detected between 1-OHNA and 1-OHP.

Logistic regression analysis of urinary OH-PAHs levels and prenatal anxiety symptoms

The information presented in Table 2 reveals the relationship between the components of OH-PAHs found in pregnant women's urine and the occurrence of prenatal anxiety symptoms. In crude models, 2-OHNA, 9-OHFLU, ∑OHFLU, 2-OHDBF and ∑OH-PAHs had statistically significant positive associations with the risk of prenatal anxiety symptoms. After controlling for confounding factors, we noted that pregnant women with the highest 2-OHNA, 9-OHFLU, ∑OHFLU, 2-OHDBF and ∑OH-PAHs concentrations had a higher likelihood of prenatal anxiety symptoms than those in the lowest tertiles (OR = 1.915, 95%CI: 1.271–2.886; OR = 2.084, 95%CI: 1.358–3.199; OR = 2.055, 95%CI: 1.355–3.117; OR = 1.675, 95%CI: 1.119–2.507; OR = 1.870, 95%CI: 1.228–2.847, respectively). We observed significant dose–response relationships between increased concentrations of 2-OHNA, 9-OHFLU, ∑OHFLU, 2-OHDBF and ∑OH-PAHs and increased risk of prenatal anxiety symptoms (P-Trend < 0.05).

BKMR analysis of urinary OH-PAHs mixture and prenatal anxiety symptoms

As seen in Fig. 2A, there was a significant trend of increasing likelihood of prenatal anxiety symptoms with increasing levels of the urinary OH-PAHs mixture compared to the 50th percentile. Figure 2B illustrates the association between the individual components of OH-PAHs in urine and the likelihood of developing prenatal anxiety symptoms. When all other OH-PAHs components in urine were fixed at median concentrations, the concentrations of 9-OHFLU and 2-OHDBF were positively associated with prenatal anxiety symptoms. After adjusting all the other OH-PAHs components in urine to the 50th, or 75th percentile, 9-OHFLU and 2-OHDBF were found to have a significant positive association with the likelihood of developing prenatal anxiety symptoms (Fig. 2C). According to the PIP values generated by the

Table 1 Basic characteristics of study participants ($n=642$)

Characteristics	Cases ($n=279$)	Controls ($n=363$)	*P*-value
	N (%)	*N* (%)	
Age, mean ± SD, years	28.29 ± 4.50	29.15 ± 3.99	**0.012**
Gestational week, mean ± SD, weeks	18.37 ± 7.96	22.22 ± 8.21	< **0.001**
Pre-pregnancy BMI(kg/m^2)			
< 18.5	31 (11.11)	43 (11.85)	0.913
18.5 ~ 24.0	172 (61.65)	218 (60.06)	
≥ 24.0	76 (27.24)	102 (28.10)	
Type of residential location			
Urban	195 (69.89)	271 (74.66)	0.180
Rural	84 (30.11)	92 (25.34)	
Marital status			
Married	269 (96.42)	353 (97.25)	0.549
Other	10 (3.58)	10 (2.75)	
Annual household income after tax(CNY)			
< 50 000	42 (15.05)	44 (12.12)	0.502
50 000 ~ 99 999	87 (31.18)	106 (29.20)	
100 000 ~ 199 999	113 (40.50)	167 (46.01)	
≥ 200 000	37 (13.26)	46 (12.67)	
Level of education			
Junior high school or below	91 (32.62)	161 (44.35)	**0.003**
Senior high school or technical secondary school	62 (22.22)	82 (22.59)	
College or above	126 (45.16)	120 (33.06)	
Occupational status during pregancy			
Out of work	159 (56.99)	217 (59.78)	0.735
Full-time	106 (37.99)	127 (34.99)	
Other	14 (5.02)	19 (5.23)	
Pregnancy intention			
Intentional pregnancy	195 (69.89)	286 (78.78)	**0.010**
Unintentional pregnancy	84 (30.11)	77 (21.21)	
Gravidity			
1	80 (28.67)	105 (28.93)	0.944
≥ 2	199 (71.33)	258 (71.07)	
History of adverse pregnancy			
Yes	56 (20.07)	37 (10.19)	< **0.001**
No	223 (79.93)	326 (89.81)	
Tobacco exposure[a]			
Yes	30 (10.75)	31 (8.54)	0.343
No	249 (89.25)	332 (91.46)	
Infertility			
Yes	12 (4.30)	13 (3.58)	0.640
No	267 (95.70)	350 (96.42)	
History of perinatal disease			
Yes	9 (3.23)	12 (3.31)	0.955
No	270 (96.77)	351 (96.69)	
Total	279 (100.00)	363 (100.00)	

Abbreviation: SD Standard deviation

[a] Tobacco exposure includes active smoking and passive smoking

Table 2 Associations between SG-adjusted urinary PAHs metabolites and prenatal anxiety symptoms ($n=642$)

OH-PAHs	Tertiles of OH-PAHs (ng/mL SG-adjusted)			*P*-Trend[c]
	Tertile 1	Tertile 2	Tertile 3	
2-OHNA	≤ 0.993	0.993–2.301	> 2.301	
n (cases/controls)	67/121	73/121	139/121	
OR[a] (95%CI)	1.000 (reference)	1.090 (0.718, 1.652)	**2.075 (1.411, 3.050)**	**< 0.001**
OR[b] (95%CI)	1.000 (reference)	1.031 (0.664, 1.602)	**1.915 (1.271, 2.886)**	**0.001**
2-OHFLU	≤ 0.483	0.483–0.850	> 0.850	
n (cases/controls)	87/121	94/121	98/121	
OR[a] (95%CI)	1.000 (reference)	1.080 (0.735, 1.588)	1.126 (0.768, 1.652)	0.559
OR[b] (95%CI)	1.000 (reference)	1.062 (0.705, 1.601)	0.983 (0.651, 1.483)	0.885
9-OHFLU	≤ 0.336	0.336–0.796	> 0.796	
n (cases/controls)	64/121	96/121	119/121	
OR[a] (95%CI)	1.000 (reference)	**1.500 (1.001, 2.248)**	**1.859 (1.253, 2.759)**	**0.004**
OR[b] (95%CI)	1.000 (reference)	1.340 (0.873, 2.056)	**2.084 (1.358, 3.199)**	**0.001**
∑OHFLU	≤ 0.924	0.924–1.556	> 1.556	
n (cases/controls)	69/120	79/122	131/121	
OR[a] (95%CI)	1.000 (reference)	1.126 (0.748, 1.696)	**1.883 (1.280, 2.769)**	**< 0.001**
OR[b] (95%CI)	1.000 (reference)	1.127 (0.730, 1.738)	**2.055 (1.355, 3.117)**	**< 0.001**
2-OHDBF	≤ 0.076	0.076–0.167	> 0.167	
n (cases/controls)	77/121	61/121	141/121	
OR[a] (95%CI)	1.000 (reference)	0.792 (0.521, 1.206)	**1.831 (1.259, 2.664)**	**< 0.001**
OR[b] (95%CI)	1.000 (reference)	0.677 (0.432, 1.060)	**1.675 (1.119, 2.507)**	**0.001**
1-OHPHE	≤ 0.073	0.073–0.251	> 0.251	
n (cases/controls)	95/121	84/121	100/121	
OR[a] (95%CI)	1.000 (reference)	0.884 (0.601, 1.302)	1.053 (0.722, 1.535)	0.674
OR[b] (95%CI)	1.000 (reference)	0.769 (0.508, 1.165)	0.919 (0.613, 1.378)	0.850
2-OHPHE	≤ 0.078	0.078–0.171	> 0.171	
n (cases/controls)	86/121	79/121	114/121	
OR[a] (95%CI)	1.000 (reference)	0.919 (0.618, 1.365)	1.326 (0.910, 1.932)	0.084
OR[b] (95%CI)	1.000 (reference)	0.928 (0.609, 1.413)	1.423 (0.947, 2.139)	0.054
3-OHPHE	≤ 0.047	0.047–0.099	> 0.099	
n (cases/controls)	80/120	84/122	115/121	
OR[a] (95%CI)	1.000 (reference)	1.033 (0.695, 1.535)	1.426 (0.974, 2.087)	**0.041**
OR[b] (95%CI)	1.000 (reference)	0.864 (0.566, 1.318)	1.151 (0.759, 1.746)	0.298
∑OHPHE	≤ 0.233	0.233–0.520	> 0.520	
n (cases/controls)	87/121	88/121	104/121	
OR[a] (95%CI)	1.000 (reference)	1.011 (0.686, 1.492)	1.195 (0.817, 1.748)	0.317
OR[b] (95%CI)	1.000 (reference)	0.879 (0.580, 1.334)	1.068 (0.709, 1.609)	0.627
1-OHP	≤ 0.060	0.060–0.196	> 0.196	
n (cases/controls)	100/121	97/121	82/121	
OR[a] (95%CI)	1.000 (reference)	0.970 (0.666, 1.413)	0.820 (0.558, 1.206)	0.296
OR[b] (95%CI)	1.000 (reference)	0.902 (0.604, 1.347)	0.873 (0.577, 1.322)	0.541
∑OH-PAHs	≤ 3.172	3.172–5.892	> 5.892	
n (cases/controls)	64/120	88/121	127/122	
OR[a] (95%CI)	1.000 (reference)	1.364 (0.906, 2.053)	**1.952 (1.319, 2.889)**	**0.001**
OR[b] (95%CI)	1.000 (reference)	1.312 (0.850, 2.025)	**1.870 (1.228, 2.847)**	**0.003**

Abbreviations: OR odds ratio, *CI* confidence interval, *SG* urine specific gravity, *2-OHNA* 2-hydroxynaphthalene, *2-OHFLU* 2-hydroxyfluorene, *9-OHFLU* 9-hydroxyfluorene, *2-OHDBF* 2-hydroxydibenzofuran, *1-OHPHE* 1-hydroxyphenanthrene, *2-OHPHE* 2-hydroxyphenanthrene, *3-OHPHE* 3-hydroxyphenanthrene, *1-OHP* 1-hydroxypyrene, ∑*OHFLU* included 2-OHFLU and 9-OHFLU, ∑*OHPHE* included 1-OHPHE, *2-OHPHE* and 3-OHPHE, ∑*OH-PAHs* included 2-OHNA, ∑*OHFLU* 2-OHDBF, ∑OHPHE and 1-OHP

[a] unadjusted odds ratio

[b] adjusted age, gestational week, level of education, pregnancy intention, history of adverse pregnancy and tobacco exposure

[c] Trend test: estimated by treating median values of OH-PAHs categories as continuous variables. Certain urinary OH-PAHs with detection rate less than 50% were excluded from the regression analyses

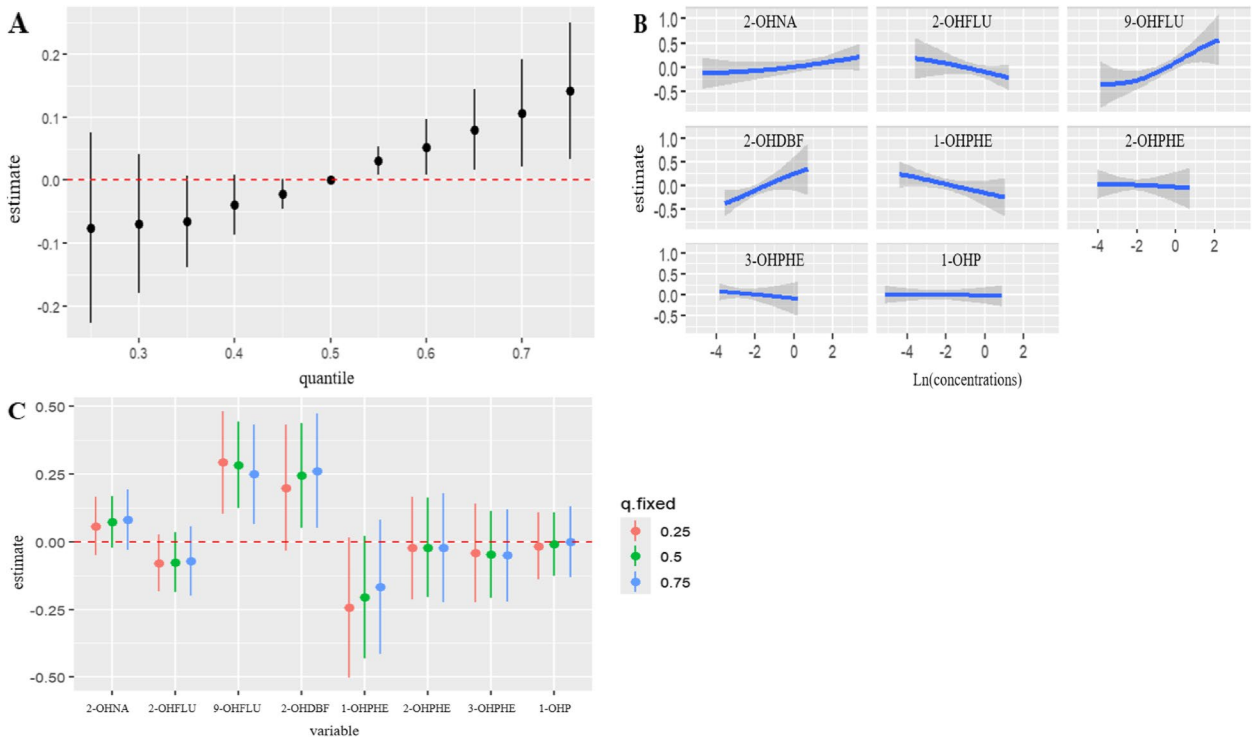

Fig. 2 Dose-response relationships of urinary OH-PAHs with risk of prenatal anxiety symptoms based on BKMR models ($n = 642$). **A** The overall relationship between the mixture of OH-PAHs in urine and prenatal anxiety symptoms. The estimated effects were assessed when the mixture of OH-PAHs was at one percentile compared to the 50th percentile. The y-axis represents the estimated effect size (risk of anxiety symptoms), and the x-axis represents the concentration of PAHs metabolites (percentiles). **B** Dose–response relationships between individual OH-PAHs components and prenatal anxiety symptoms. The estimated effects were assessed when all other OH-PAHs components were fixed at their median concentrations. The y-axis represen ts the estimated effect size (risk of anxiety symptoms), and the x-axis represents the Ln-transformed concentrations of PAH metabolites.**C** Latent continuous outcome when individual urinary OH-PAHs were at the 75th vs 25th percentile, while all other OH-PAHs components were fixed at the 25th, 50th or 75th percentile. The y-axis represents the estimated effect size (risk of anxiety symptoms), and the x-axis represents the specific PAH concentrations (P25, P50, and P75). The BKMR models were adjusted for age, gestational week, level of education, pregnancy intention, history of adverse pregnancy and tobacco exposure. Urinary OH-PAHs concentrations were Ln-transformed. Metabolites with detection rates less than 50% were excluded from the analyses. Abbreviations: 2-OHNA: 2-hydroxynaphthalene; 2-OHFLU: 2-hydroxyfluorene; 9-OHFLU: 9-hydroxyfluorene; 2-OHDBF: 2-hydroxydibenzofuran; 1-OHPHE: 1-hydroxyphenanthrene; 2-OHPHE: 2-hydroxyphenanthrene; 3-OHPHE: 3-hydroxyphenanthrene; 1-OHP: 1-hydroxypyrene

BKMR model (Table S4), the PIP values ranged from 0.091 to 0.836, with 9-OHFLU showing the highest value of 0.836.

Logistic regression analysis of urinary OH-PAHs levels and postpartum anxiety symptoms

Additionally, we also analyzed the association between the concentrations of PAHs metabolites in urine during pregnancy and postpartum and postpartum anxiety symptoms. We found that medium levels of 2-OHFLU and high levels of ∑OHFLU in prenatal urine were positively associated with postpartum anxiety symptoms (OR = 2.101, 95%CI: 1.000–4.414 for the medium vs. low 2-OHFLU exposure; OR = 2.277, 95%CI: 1.080–4.799 for the high vs. low ∑OHFLU exposure) (Table 3). Nevertheless, our analysis did not reveal any significant association between the concentrations of PAH metabolites in postpartum urine and the occurrence of postpartum anxiety symptoms (Table S5).

Discussion

To the best of our knowledge, there have been many studies that have reported harmful health effects from exposure to PAHs, while the existing literature regarding the relationship between PAH exposure and the probability of developing perinatal anxiety symptoms remains limited. In the present study, we performed a primary care-based, case–control study including 279 pregnant women with prenatal anxiety symptoms (cases) and 363 pregnant women (controls) to evaluate how PAH exposure relates to perinatal anxiety symptoms. We found that higher concentrations levels of 2-OHDBF, ∑OHFLU, ∑OH-PAHs, 2-OHNA, and 9-OHFLU were positively associated with prenatal

Table 3 Logistic regression analysis of the effects of PAHs exposure during pregnancy on anxiety symptoms at 42 days postpartum ($n = 230$)

OH-PAHs	Concentrations of PAH metabolites			*P*-trend
	Low	medium	High	
2-OHNA				
OR[a] (95%CI)	1.000 (reference)	1.687 (0.892, 3.193)	1.562 (0.825, 2.960)	0.170
OR[b] (95%CI)	1.000 (reference)	1.791 (0.859, 3.736)	1.487 (0.694, 3.185)	0.296
2-OHFLU				
OR[a] (95%CI)	1.000 (reference)	**2.040 (1.072, 3.885)**	1.523 (0.805, 2.882)	0.198
OR[b] (95%CI)	1.000 (reference)	**2.101 (1.000, 4.414)**	1.299 (0.621, 2.717)	0.489
9-OHFLU				
OR[a] (95%CI)	1.000 (reference)	1.447 (0.766, 2.734)	1.699 (0.894, 3.227)	0.106
OR[b] (95%CI)	1.000 (reference)	1.390 (0.661, 2.923)	1.735 (0.814, 3.697)	0.154
∑OHFLU				
OR[a] (95%CI)	1.000 (reference)	1.752 (0.921, 3.334)	**2.279 (1.192, 4.356)**	**0.013**
OR[b] (95%CI)	1.000 (reference)	1.800 (0.853, 3.798)	**2.277 (1.080, 4.799)**	**0.031**
2-OHDBF				
OR[a] (95%CI)	1.000 (reference)	0.852 (0.449, 1.617)	**2.295 (1.198, 4.398)**	**0.013**
OR[b] (95%CI)	1.000 (reference)	0.754 (0.360, 1.575)	2.114 (0.996, 4.484)	0.059
1-OHPHE				
OR[a] (95%CI)	1.000 (reference)	**0.416 (0.217, 0.797)**	0.745 (0.393, 1.412)	0.375
OR[b] (95%CI)	1.000 (reference)	**0.399 (0.186, 0.858)**	0.800 (0.382, 1.673)	0.563
2-OHPHE				
OR[a] (95%CI)	1.000 (reference)	0.660 (0.349, 1.247)	1.054 (0.557, 1.994)	0.871
OR[b] (95%CI)	1.000 (reference)	0.656 (0.314, 1.373)	0.994 (0.472, 2.094)	0.998
3-OHPHE				
OR[a] (95%CI)	1.000 (reference)	1.138 (0.603, 2.149)	1.440 (0.764, 2.716)	0.260
OR[b] (95%CI)	1.000 (reference)	1.103 (0.530, 2.299)	1.322 (0.638, 2.739)	0.453
∑OHPHE				
OR[a] (95%CI)	1.000 (reference)	0.545 (0.287, 1.035)	0.855 (0.453, 1.612)	0.629
OR[b] (95%CI)	1.000 (reference)	0.483 (0.229, 1.021)	0.793 (0.379, 1.658)	0.545
1-OHP				
OR[a] (95%CI)	1.000 (reference)	0.812 (0.431, 1.529)	0.790 (0.419, 1.491)	0.467
OR[b] (95%CI)	1.000 (reference)	1.185 (0.574, 2.449)	0.824 (0.392, 1.732)	0.623
∑OHPAH				
OR[a] (95%CI)	1.000 (reference)	1.054 (0.559, 1.986)	1.564 (0.826, 2.959)	0.170
OR[b] (95%CI)	1.000 (reference)	1.258 (0.601, 2.635)	1.716 (0.808, 3.644)	0.160

Abbreviations: OR Odds ratio, *CI* Confidence interval, *2-OHNA* 2-hydroxynaphthalene, *2-OHFLU* 2-hydroxyfluorene, *9-OHFLU* 9-hydroxyfluorene, *2-OHDBF* 2-hydroxydibenzofuran, *1-OHPHE* 1-hydroxyphenanthrene, *2-OHPHE* 2-hydroxyphenanthrene, *3-OHPHE* 3-hydroxyphenanthrene, *1-OHP* 1-hydroxypyrene, ∑*OHFLU* included 2-OHFLU and 9-OHFLU, ∑*OHPHE* included 1-OHPHE, 2-OHPHE and 3-OHPHE, ∑*OH-PAHs* included 2-OHNA, ∑*OHFLU* 2-OHDBF ∑OHPHE and 1-OHP

[a] unadjusted odds ratio

[b] adjusted age, gestational week, level of education, pregnancy intention, history of adverse pregnancy and tobacco exposure. The level of OH-PAHs concentrations in urine were Ln-transformed. Certain urinary OH-PAHs with detection rate less than 50% were excluded from the regression analyses

anxiety symptoms. Furthermore, the results revealed that gestational exposure to 2-OHFLU and ∑OHFLU was significantly linked to a heightened likelihood of postpartum anxiety symptoms.

Exposure to PAHs among pregnant women is widespread (Table S6). In comparison to the detection results of other relevant studies [13, 17, 26, 28], the average median concentrations of OH-PAHs components in pregnant women's urine in the present study were low. The median concentration of 2-OHNA in pregnant women's urine in the present study (1.845 ng/mL) was lower than those reported among pregnant women in Czech (3.3 ng/mL) [28], Brazil (2.28 ng/mL) [26], and Shanghai, China (4.48 ng/mL) [13], except for Wuhan,

China (1.43 ng/mL) [17]. In our study, the median concentration of 2-OHFLU in the urine of pregnant women was 0.667 ng/mL. This value was higher than the concentrations reported in the Czech Republic (0.23 ng/mL) and Wuhan, China (0.49 ng/mL), yet lower than those reported in Brazil (3.67 ng/mL) and Shanghai, China (1.65 ng/mL). Regarding the median concentrations of urinary 1-OHP, 3-OHPHE, and 2-OHPHE, in the present study, they were measured at 0.116 ng/mL, 0.064 ng/mL, and 0.127 ng/mL, respectively. These values were comparable to those reported in Wuhan, China (0.03, 0.10, and 0.11 ng/mL, respectively), but lower than the concentrations reported in Shanghai, China (1.19, 1.13, and 0.51 ng/mL, respectively). In recent years, with the improvement of air pollution in China, the PAHs exposure level in non-smoking general population has decreased [8]. Additionally, traffic pollution is the main source of PAHs exposure for pregnant women [13]. Due to the differences in city size and traffic flow, there are significant differences in PAHs exposure levels among cities [4].

PAHs exposure has adverse effects on mood disorders. Several epidemiological studies have explored the link between the exposure level to PAHs and likelihood of developing anxiety symptoms in children and occupational populations [19],Wang, 2020). Perera et al. found that higher levels of PAHs exposure during pregnancy increased the likelihood of developing anxiety symptoms in children [19]. In 2017, Wang et al. measured PAHs metabolites levels in the urine of 652 male miners in China and found no link between PAHs exposure and anxiety [30]. In this study, we found that concentrations levels of 2-OHNA, 9-OHFLU, ∑OHFLU, ∑OH-PAHs and 2-OHDBF were associated with the likelihood of developing prenatal anxiety symptoms. In addition, we followed 230 women up to 42 days postpartum (44 anxiety symptoms cases and 186 controls) and found higher concentrations of ∑OHFLU in pregnancy urine were associated with higher likelihood of developing postpartum anxiety symptoms. However, the follow-up rate of our study was low (35.83%), and future longitudinal studies from other regions are needed to validate our findings.

We investigated the effect of combined PAH exposure on prenatal anxiety symptoms using the BKMR model and interestingly found that the concentration of OH-PAHs mixture in pregnant women's urine was significantly and positively correlated with the likelihood of prenatal anxiety symptoms (Fig. 2A). Notably, our results indicated a positive correlation between mixtures of OH-PAHs at the 55th percentile and above and the likelihood of developing prenatal anxiety symptoms compared to all OH-PAHs components in urine fixed at the 50th percentile (Fig. 2A). These findings indicated that there may be a potential cut-off value for PAHs exposure levels and the likelihood of developing prenatal anxiety symptoms. Future studies should expand this scope to elucidate the dose–response relationship between PAHs exposure levels and the likelihood of developing mood disorders in different populations, which could offer valuable epidemiological insights that can inform the development of effective environmental protection measures. In addition, we found a significant positive effect of urinary 9-OHFLU on prenatal anxiety symptoms when all of the other components of OH-PAHs in urine were fixed at their 25th, 50th or 75th percentile (Fig. 2C). At the same time, we fixed all other components of OH-PAHs in urine at a median concentration and found that 9-OHFLU concentration was positively associated with the likelihood of prenatal anxiety symptoms (Fig. 2B). These results indicated that the relationship between the level of 9-OHFLU in urine and the likelihood of developing prenatal anxiety symptoms is stable, independent of other OH-PAHs. Reducing exposure to fluorene (the prototype of 9-OHFLU) may help reduce the likelihood of developing prenatal anxiety symptoms.

Laboratory studies suggest that PAHs exposure may lead to detrimental effects on anxiety symptoms [18, 24]. Researchers have revealed that PAHs compounds upregulate cytochrome P450 1A through aromatic receptor (AhR)-dependent signaling pathways [24], thereby increasing lipid peroxidation and protein carbonization in the brain, which in turn influence the occurrence of anxiety in zebrafish [18]. Additionally, mitochondrial DNA may be a potential pathway for PAHs-mediated anxiety symptoms in adults. The researchers reported that exposure to environmental PAHs can decrease the mitochondrial DNA copy number in non-smoking Chinese women [32].

To the best of our knowledge, our study is the first to report the link between PAHs exposure and the likelihood of developing perinatal anxiety symptoms. However, there are some limitations that need to be mentioned. Firstly, this is a case–control design that recruited a relatively small number of pregnant women, which may have an impact on the accuracy of the final results and limit the representativeness of the findings. Secondly, the assessment of anxiety symptoms in this study was based on the GAD-7 scale rather than clinical diagnosis. However, relevant studies have reported that the GAD-7 scale has internal consistency and reliability in screening for perinatal anxiety symptoms [11, 25]. Moreover, the representativeness of the results may be limited as this study only included participants from two community hospitals in Hefei, China. Therefore, multi-center longitudinal cohort studies are required to conduct a more in-depth

exploration of the adverse impacts of PAHs exposure on perinatal mood disorders. Finally, a notable limitation of our study is the absence of direct assessment regarding the potential contribution of self-exposure to cooking fumes on personal PAHs exposure levels among pregnant women. Nevertheless, the proportion of women who cook during pregnancy in China has significantly decreased [12], suggesting that cooking fume exposure may represent a relatively minor contributor to overall PAHs exposure in this population.

Conclusion

In conclusion, the evidence provided by this study suggests that PAHs are linked to a heightened probability of experiencing perinatal anxiety symptoms. The detrimental impact of environmental exposure on perinatal mental health should be further explored in the future.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author' contributions
MJ and FT conceived and designed the study. HZ, BZ, and YJ are responsible for the overall content as guarantor, participated in data collection and performed statistical analyses. HZ and BZ wrote the first draft of the manuscript. YJ, FH, HC, ML, and SW contributed to detection of the urine samples. ML, HL, YG, YH, XY, FZ, and MS were involved in the collection and transfer of the urine samples. All authors contributed to revisions of the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted under the guidance of the Declaration of Helsinki, and all participants in this study filled in informed consent forms at the time of recruitment. This study has been approved by the Ethics Committee of Anhui Medical University (No: 83220006).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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