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Polycyclic aromatic hydrocarbons are associated with sleep-related disorders in adults: the potential mediating role of inflammation

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Abstract

Background The evidence on the effects of polycyclic aromatic hydrocarbons (PAHs) on sleep disorders is limited. This study aimed to explore the association between PAH exposure and sleep-related disorders, and the potential mediating roles of inflammation in these relationships were further been examined.

Methods This study utilized data from adult participants (≥ 20 years of age) in the US National Health and Nutrition Examination Survey 2005–2008. Weighted logistic regression models were used to estimate the associations between each urinary PAH biomarker and sleep-related disorders. Structural Equation Modelling (SEM) was applied to evaluate the association between PAH exposure and sleep-related disorders and to assess the mediating effect of inflammatory markers that include C-reactive protein (CRP) and white blood cell counts (WBC).

Results One or more urinary PAH metabolites were associated with an increased risk of long sleep-onset latency, obstructive sleep apnea (OSA), sleep problems, and daytime sleepiness. The latent PAH exposure variable in SEM was positively associated to long sleep-onset latency ($\beta = 0.054$, $p = 0.035$), OSA ($\beta = 0.071$, $p = 0.002$), sleep problems ($\beta = 0.089$, $p < 0.001$) and daytime sleepiness ($\beta = 0.066$, $p = 0.003$). Mediation analysis suggested that WBC mediated the link between PAH exposure and sleep problems (Indirect effect = 0.009, 95%CI: 0.002 ~ 0.017, Proportion: 10.8%), as well as daytime sleepiness (Indirect effect = 0.011, 95%CI: 0.005 ~ 0.019, Proportion: 15.7%).

Conclusions PAH exposure was associated with an increased risk of long sleep-onset latency, obstructive sleep apnea, sleep problems, and daytime sleepiness. Inflammation may be one potential mechanism by which PAH exposure contributes sleep problems and daytime sleepiness.

Keywords Sleep-related disorders, Inflammation, C-reactive protein, White blood cells counts, Polycyclic aromatic hydrocarbons

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Background

Poor sleep is emerging as an important public health issue raising a considerable amount of concern. Nearly one-third of adults have various sleep problems and lack of adequate sleep in the United States [1], and the percentage in China was about 40%. The sleep-related disorders, such as poor sleep quality, insomnia, insufficient sleep, and sleep apnea, have been reported in association with a variety of health issues, such as diabetes [2], cardiovascular disease [3], cancers [4, 5], cognitive decline [6] and mental disorders [7]. Recently, sleep-related disorders have been considered another adverse health outcome associated with environmental pollution. A large group of emerging research has concentrated on the impacts of environmental exposure such as air pollution, second-hand smoke, heavy metals, and noise pollution on sleep health [8].

Polycyclic aromatic hydrocarbons (PAHs) refer to a substantial number of environmental pollutants that developed as a result of the pyrolysis or incomplete burning of organic materials [9, 10]. Prior research studies have linked PAH exposure to a variety of adverse health effects, such as cardiovascular diseases [11], diabetes [12], reduced lung function [13], and cancers [14]. However, there is limited evidence of the association between PAH exposure and sleep disorders. Furthermore, the underlying mechanisms of the association between exposure and sleep disorders remain largely unclear.

Numerous studies have revealed a significant correlation between PAH exposure and elevated levels of inflammatory indicators, such as white blood cell counts (WBC) or C-reactive protein (CRP) levels [15], and could cause health damage by promoting oxidative stress and inflammatory processes [16, 17]. A recent study revealed that PAHs might have toxic effects on the adolescent female liver, and the inflammation-mediated this association [18]. However, it remains unclear whether the link between PAH exposure and sleep disorders is also mediated by inflammation.

Therefore, the purpose of this study was to investigate the relationship between PAH metabolites and sleep-related disorders, such as abnormal sleep-onset latency (lengthen or shorten), sleep problems, obstructive sleep apnea (OSA), and daytime sleepiness. In addition, we further explored whether inflammatory markers (including CRP levels and WBC), mediated these relationships.

Material and methods

Study population

The data for the present study were obtained from the National Health and Nutrition Examination Survey (NHANES)(http://www.cdc.gov/nchs/nhanes.htm). The data of NHANES 2005–2006 and 2007–2008 were utilized to determine outcomes and perform analyses in this study, as these were the only cycles in which participants' sleep-related habits or problems were investigated in detail. The data from NHANES 2005–2006 and NHANES 2007–2008 were combined to increase the sample size. In-home interviews were used to collect comprehensive information on the participants' demographic, socioeconomic, medical, and sleep characteristics. Those participants who agreed to an in-home interview were then invited to undergo a physical examination, which included collecting urine and blood, at mobile examination centers (MECs). PAH metabolites were measured in a randomly selected one-third subsample of the selected data set. The protocol of NHANES was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board and written consent was obtained from each participant. The flowchart of variables selection was presented in Fig. 1.

Assessment of sleep disorders

In this study, sleep disorders refer to a set of four specific sleep-related outcomes assessed independently: sleep onset latency, obstructive sleep apnea, sleep problems, and daytime sleepiness [19]. These four dimensions were analyzed separately to capture different aspects of sleep health.

Sleep-onset latency: Sleep onset latency was categorized as short (≤ 5 min/night), normal (6~30 min/night), or long (> 30 min/night), based on participants' responses to the question: "How long to fall asleep (minutes)?".

Obstructive sleep apnea: Obstructive sleep apnea was identified if any one of the following criteria was met: (1) sleep apnea diagnosed by a doctor; (2) snoring 3 or more nights per week; (3) snorting, gasping, or stopping breathing 3 or more nights per week; or (4) feeling excessively sleepy during the day 16-30 times per month despite sleeping around 7 or more hours per night on weekdays or work nights [19, 20].

Sleep problems: Sleep problems were defined based on responses to four self-reported symptoms. Participants were considered to have sleep problems if they answered "often" (≥ 5 times/month) or more to any of the following: (1) have been told have trouble sleeping by a doctor or other health professional; (2) had trouble falling asleep in the past month; (3) woke up during the night and had trouble getting back to sleep in the past month; or (4) woke up too early in the morning and were unable to get back to sleep in the past month [19, 21].

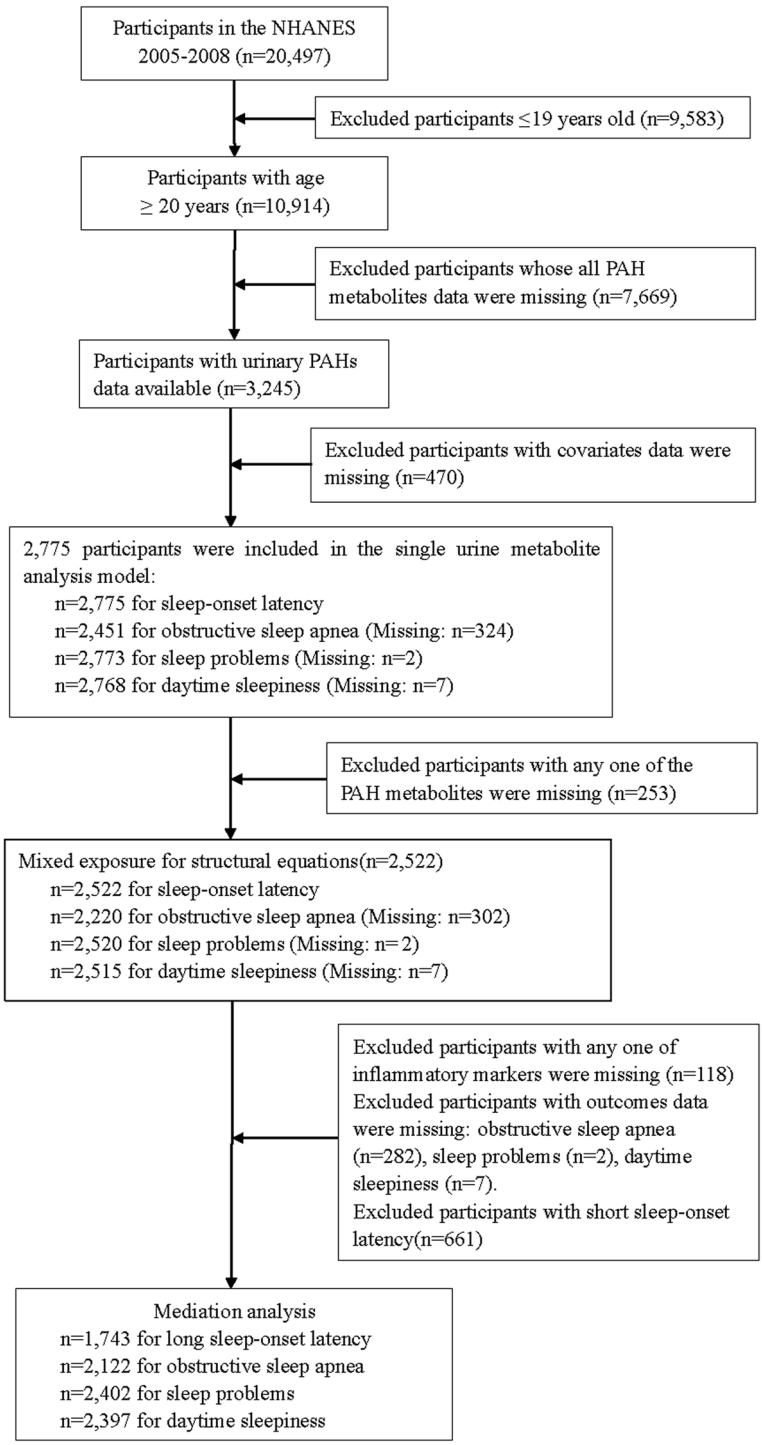

Fig. 1 The flowchart of variables selection

Daytime sleepiness: Daytime sleepiness was defined as reporting any of the following symptoms occurring "often" or more frequently (i.e., ≥ 5 times per month) during the past month: (1) feeling unrested during the day, no matter how many hours of sleep they had; or (2) feel excessively or overly sleepy during the day [19, 21].

Measurements of urinary PAHs

Nine urinary PAH metabolites markers were considered in the present study, including 1-hydroxynaphthalene (1-Nap), 2-hydroxynaphthalene (2-Nap), 2-hydroxyfluorene (2-Flu), 3-hydroxyfluorene (3-Flu),1-hydroxyphenanthrene (1-Phe), 2-hydroxyphenanthrene (2-Phe), 3-hydroxyphenanthrene (3-Phe), 1-hydroxypyrene (1-Pyr), and 9-hydroxyfluorene (9-Flu). Urine was collected from individuals and then processed and stored at −20 °C until it was transported to the lab for testing. The levels of urinary PHAs metabolites were measured using isotope dilution capillary gas chromatography-tandem mass spectrometry (GC–MS/MS) (details see at: https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2007). Urinary PAH concentrations were substituted by the square root of two when which were below the lower limit of detection (LLOD).

Measurement of Inflammation

In this study, we considered two inflammatory markers: white blood cell counts (WBC) and C-reactive protein (CRP). The methods used to complete the WBC was based on the Beckman Coulter method, and results were expressed as 1,000 cells/μL. Latex-enhanced nephelometry was applied to measure the level of CRP. Mouse monoclonal anti-CRP antibodies, covalently linked to latex particles, were mixed with serum samples and then an automatic blank subtraction was performed, and CRP concentrations were calculated by using a calibration curve. A detailed description of the laboratory method could be found on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2007).

Covariates

The information including demographic, anthropometric, lifestyle, health information, and occupation was considered covariates enrolled in the analytical model. The demographic information included age, gender, race/ethnicity, marital status, education level, and income level (poverty income ratio, PIR).

Body mass index (BMI) was calculated by the weight divided by height squared (kg/m^2), which was categorized into four types in this study as follows: < 18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥ 30. Alcohol use was classified as drinking (≥ 4 drinks per week) and non-drinking (< 4 drinks per week). Cigarette use was categorized as smoking (≥ 100 cigarettes in life) and non-smoking (< 100 cigarettes in life).

Diabetes and hypertension, as well as cardiovascular diseases (CVD), were also covariates included in the analysis model. Diabetes and hypertension, on the basis of the health diagnosis by a doctor or other health professional, were categorized as a binary variable(yes/no), in which borderline diabetes was also classified as no diabetes. Participants were defined as having CVD if they had a positive response to any health problems as follows: "coronary heart disease", "congestive heart failure", "angina/angina pectoris", "heart attack", or "stroke". Working status or schedule, as a major factors affecting sleep health, was considered an important covariate in this study. The work status was categorized into three types according to the current work of participants: (1) not working, referring to not working at a job or business or seeking work; (2) regular daytime schedule, referring to working at a job or business during regular daylight hours; and (3) regular night shift or rotating shift, referring to presently employed in a position or business with a regular evening shift, rotating shift, or other schedules [19].

Statistical analysis

Weighted analyses with subsample weights, primary sampling units and strata, were applied to consider account for the complex sampling design.

First, $\log_{10}$-transformation was conducted for urinary PAH metabolite concentrations to reduce the influence of extreme value and skewness distribution, and then they were divided into four equal parts on the basis of the quantiles. Next, multivariable logistic regression models with weights, adjusted for covariates including age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and creatinine, were performed to evaluate the association between the level of each urinary PAH metabolites and sleep-related disorders, respectively. Furthermore, the quartile variable of each urinary PAH metabolite concentrations was considered as continuous to estimate the p-values for trend.

The Pearson correlation was used to assess correlations between nine urine PAH metabolites (Log-transformed). Structural Equation Modelling (SEM) was used to estimate separately the association between PAH exposure and sleep-related disorders [22]. SEM addressed the limitations of collinearity of multiple exposure indicators in regression models [23] and has been reported to have potential application value in environmental

epidemiological [24]. In the current analysis, we constructed a latent construct, consisting of nine urinary metabolite concentrations (Log-transformed), to represent PAH exposure. Similar methods were used in previous studies [25]. Since not all individuals had complete urinary PAH metabolite concentrations, when analyzing the association between PAHs exposure and sleep-related disturbances, participants were excluded from the analysis if one of the PAH metabolites were not measured.

In addition, structural equation models, with latent urinary PAH exposure as the predictor, four sleep-related disorders as outcomes, and inflammatory markers (CRP levels and white blood cell counts) as mediators, were constructed to estimate the mediating effect after adjusting a series of potential covariates. Participants with short sleep-onset latency (≤ 5 min, n = 661) were excluded from the mediation analysis, as our primary regression results showed no significant association between PAH exposure and short sleep latency. The mediation analysis was therefore restricted to individuals with long sleep latency to reflect the relevant exposure-outcome relationship. The bootstrapping method with 95% bias-corrected accelerated confidence intervals (CIs), based on 5000 bootstrap samples, was applied to estimate the indirect effect [26]. Several fit indices, including comparative fit index (CFI ≥ 0.90), normed fit index (NFI ≥ 0.90), root mean square error approximation (RMSEA < 0.10), and standardized root mean square residual (SRMSR < 0.08), were used to evaluate models fit [27]. All analytical models included urinary creatinine as a covariate to adjust for urine dilution.

As a sensitivity analysis, we applied the Weighted Quantile Sum (WQS) regression to assess the combined effect of PAH metabolite mixtures on sleep outcomes. The model constructed a WQS index to estimate the mixture effect of environmental chemical exposures on the outcome, and evaluated the contribution of each environmental chemical to the overall index effect through the relative strength of weights assigned to each variable [28]. In this study, the WQS index for PAH mixture exposure was constructed based on urine metabolites, with 40% of the data used as the test set and the remaining 60% for validation set. There were 1000 bootstrap steps in the multivariable regression models. Given the positive correlations between the PAH components and outcomes shown in the single-pollutant models, only positive associations were considered in the WQS model.

Logistic regression models were conducted in R version 4.1.3 (R Core Team, 2022), and analyses were performed using the survey estimation commands in "svyglm" to account for sampling weights. The WQS regression was performed by the R package "gWQS" (version 3.0.5). Structural Equation Modelling (SEM) was constructed by IBM SPSS Amos 21.0 version (IBM Corporation, Armonk, NY, USA). A two-sided p-value < 0.05 was considered statistically significant.

Results

Basic characteristics

Table 1 presents the characteristics of 2,775 participants. The participants' weighted average age (standard deviation) was 46.4 (16.4) years. Among the participants, 48.4% were male and 72.0% were Non-Hispanic whites. The means (standard deviation) of nine urinary PAH metabolite levels (log-transformed) were ranged from 1.8 (0.3) to 3.6 (0.5) μg/L (Table 1). Approximately 16.8% of participants reported taking more than 30 min to fall asleep, whereas 28.7% reported falling asleep within 5 min. Nearly half of the participants (49.5%) reported symptoms suggestive of obstructive sleep apnea. About 39.8% of individuals reported having sleep problems, such as difficulty falling asleep, waking up during the night, or waking up too early in the morning. In addition, 28.3% of participants reported feeling excessively sleepy during the day.

Associations between specific urinary PAH metabolites and sleep-related disorders

Table 2 shows the association between nine urinary PAH metabolite levels and sleep-onset latency among US adults. Multivariable logistic regression analyses, using log-transformed urinary PAH monomers, suggested that, compared with the lowest quartile, the participants in the highest quartile of urinary3-Flu (OR = 1.77, 95%CI: 1.14 ~ 2.74) and 2-Flu (OR = 1.66, 95%CI: 1.01 ~ 2.73) concentrations had an increased risk of long sleep-onset latency and those associations showed a linear trend, after adjusting for age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and creatinine. The participants in the third quartiles of urinary 2-Nap and 9-Flu concentrations also had higher odds of long sleep-onset latency compared to those in the lowest quartile, with OR (95%CI) of 2.12 (1.37 ~ 3.28) and 1.61 (1.03 ~ 2.52), respectively. The association between shortened sleep latency and urinary PAH monomer concentrations did not reach a significant level

The associations between nine urinary PAH metabolites and OSA, sleep problems and daytime sleepiness from adjusted logistic regression models are presented in Table 3. Compared with the lowest quartile, participants in higher quartiles of 3-Flu (quartile 2: OR = 1.60, 95%CI: 1.14 ~ 2.23; quartile 3: OR = 1.66, 95%CI: 1.25 ~ 2.19; quartile 4: OR = 1.88, 95%CI: 1.19 ~ 2.97; p for

Table 1 The characteristics of participant, NHANES 2005–2008

Characteristics	n	Means (SD) or proportions
Gender, n (%)		
Male	1354	48.4
Female	1421	51.6
Age (years), Means (SD)	2775	46.4 (16.4)
Race/ethnicity, n (%)		
Mexican American	518	8.2
Other Hispanic	184	3.6
Non-Hispanic White	1374	72.0
Non-Hispanic Black	603	11.1
Other Race	96	5.0
Education Level, n (%)		
Less Than 9th Grade	304	5.7
9-11 th Grade	451	12.3
High School Grad/ GED or Equivalent	714	26.0
Some College or AA degree	757	30.9
College Graduate or above	549	25.2
BMI (kg/m^2), n (%)		
< 18.5	46	1.8
18.5 to 24.9	768	31.0
25.0 to 29.9	925	31.9
≥ 30	1036	35.4
Marital status, n (%)		
Married/Living with partner	1758	66.8
Widowed/ Divorced/Separated	589	17.9
Never married	428	15.2
Cigarette use, n (%)		
No	1452	50.7
Yes	1323	49.3
Alcohol use, n (%)		
No	808	25.5
Yes	1967	74.5
Hypertension, n (%)		
No	1819	68.6
Yes	956	31.4
Diabetes, n (%)		
No	2478	92.1
Yes	297	7.9
Cardiovascular disease, n (%)		
No	2476	91.1
Yes	299	8.9
Work status, n (%)		
Not working	1141	30.9
Regular daytime schedule	1222	52.3
Regular evening or night shift, rotating shift, or other	412	16.8
Poverty income ratio, Means (SD)	2775	3.1 (1.6)
C-reactive protein (Log-transformation, mg/dL), Means (SD)	2664	−0.8 (0.6)
White blood cell counts (Log-transformation, cells/μL), Means (SD)	2665	0.9 (0.1)
Urine creatinine, (Log-transformation, mg/dL), Means (SD)	2775	2.0 (0.3)
PAHs (Log-transformation), Mean (SD)		
1-Hydroxynaphthalene	2680	3.5 (0.7)
2-Hydroxynaphthalene	2728	3.6 (0.5)
3-Hydroxyfluorene	2735	2.1 (0.6)
2-Hydroxyfluorene	2756	2.5 (0.5)
3-Hydroxyphenanthrene	2768	2.0 (0.4)
1-Hydroxyphenanthrene	2775	2.2 (0.3)
2-Hydroxyphenanthrene	2730	1.8 (0.3)
1-Hydroxypyrene	2737	2.0 (0.4)
9-Hydroxyfluorene	2761	2.6 (0.4)
Sleep-onset latency, n (%)		
Short	753	28.7
Normal	1476	54.5
Long	546	16.8
Obstructive sleep apnea, n (%)		
No	1096	40.6
Yes	1355	49.5
Missing	324	9.9
Sleep problems, n (%)		
No	1729	60.1
Yes	1044	39.8
Missing	2	0.1
Daytime sleepiness, n (%)		
No	2041	71.6
Yes	727	28.3
Missing	7	0.1

BMI Body mass index, *SD* Standard deviation, *n* numbers of subjects, %, weighted percentage

trend = 0.019), 2-Flu (quartile 2: OR = 1.55, 95%CI: 1.13 ~ 2.12; quartile 3: OR = 1.74, 95%CI: 1.23 ~ 2.48; quartile 4: OR = 1.80, 95%CI: 1.08 ~ 3.01; p for trend

Table 2 The multinomial logistic regressions for sleep-onset latency for adult participants in NHANES 2005–2008, odds ratios (ORs) and 95% confidence intervals (CIs)

Variable	Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
1-Nap				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	0.75 (0.51, 1.11)	0.132	1.04 (0.64, 1.69)	0.871
Quantile 3	1.12 (0.70, 1.77)	0.600	1.56 (0.97, 2.49)	0.062
Quantile 4	1.06 (0.74, 1.51)	0.729	1.42 (0.89, 2.34)	0.121
p for trend	0.358		0.051	
2-Nap				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.04 (0.70, 1.54)	0.825	1.37 (0.81, 2.32)	0.204
Quantile 3	1.11 (0.79, 1.57)	0.506	2.12 (1.37, 3.28)	0.004
Quantile 4	1.06 (0.68, 1.65)	0.769	1.54 (0.77, 3.08)	0.188
p for trend	0.680		0.053	
3-Flu				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.14 (0.81, 1.62)	0.407	1.28 (0.79, 2.06)	0.271
Quantile 3	1.04 (0.66, 1.65)	0.835	1.31 (0.88, 1.97)	0.162
Quantile 4	1.26 (0.83, 1.89)	0.237	1.77 (1.14, 2.74)	0.017
p for trend	0.371		0.010	
2-Flu				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.14 (0.73, 1.78)	0.511	1.38 (0.81, 2.37)	0.204
Quantile 3	1.28 (0.78, 2.11)	0.290	1.43 (0.87, 2.35)	0.140
Quantile 4	1.17 (0.76, 1.78)	0.430	1.66 (1.01, 2.73)	0.045
p for trend	0.410		0.027	
3-Phe				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.18 (0.76, 1.82)	0.421	1.43 (0.77, 2.64)	0.226
Quantile 3	0.99 (0.63, 1.54)	0.947	1.36 (0.85, 2.17)	0.170
Quantile 4	1.12 (0.70, 1.80)	0.585	1.28 (0.77, 2.13)	0.298
p for trend	0.837		0.369	
1-Phe				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	0.95 (0.59, 1.51)	0.795	1.25 (0.72, 2.20)	0.384
Quantile 3	1.14 (0.69, 1.90)	0.572	1.36 (0.81, 2.28)	0.213
Quantile 4	1.25 (0.75, 2.10)	0.351	1.48 (0.87, 2.52)	0.128
p for trend	0.219		0.126	
2-Phe				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.01 (0.64, 1.58)	0.979	0.99 (0.61, 1.61)	0.973
Quantile 3	0.94 (0.61, 1.46)	0.761	1.37 (0.83, 2.25)	0.192
Quantile 4	1.05 (0.70, 1.58)	0.777	1.24 (0.72, 2.10)	0.394
p for trend	0.830		0.217	
1-Pyr				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.00 (0.68, 1.46)	0.996	1.15 (0.71, 1.85)	0.523
Quantile 3	0.96 (0.63, 1.47)	0.829	1.43 (0.92, 2.22)	0.100
Quantile 4	0.96 (0.65, 1.41)	0.800	0.97 (0.58, 1.62)	0.906

Table 2 (continued)

Variable	Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
p for trend	0.736		0.917	
9-Flu				
Quantile 1	[Ref]	-	[Ref]	-
Quantile 2	1.30 (0.88, 1.91)	0.159	1.21 (0.78, 1.88)	0.341
Quantile 3	1.01 (0.66, 1.56)	0.951	1.61 (1.03, 2.52)	0.039
Quantile 4	1.18 (0.76, 1.83)	0.415	1.45 (0.86, 2.44)	0.145
p for trend	0.761		0.089	

Model 1 means short sleep-onset latency (≤ 5 min/night) *vs.* normal sleep-onset latency duration (6 ~ 30 min/night). Model 2 long sleep-onset latency (> 30 min/night) *vs.* normal sleep-onset latency duration (6 ~ 30 min/night). All models were adjusted for age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and urinary creatinine. OR (95%CI) means odds ratio and 95% confidence interval; Ref = Reference group

= 0.029), and 3-Phe (quartile 3: OR = 1.51, 95%CI: 1.06 ~ 2.14; quartile 4: OR = 1.76, 95%CI: 1.14 ~ 2.71; *p* for trend = 0.009) reported an increased risk of OSA. In addition, increased odds of OSA were observed in the participants in the highest quartile of 1-Phe (OR = 1.65, 95%CI: 1.06 ~ 2.57) and 9-Flu (OR = 1.83, 95% CI: 1.04 ~ 3.21) in the fully adjusted model.

For sleep problems, the third quartile of 2-Nap was significantly associated with increased odds (OR = 1.30, 95%CI: 1.00 ~ 1.68) compared to the lowest quartile. In terms of daytime sleepiness, after adjusting for additional covariates, the urinary concentrations of 1-Nap (quartile 3: OR = 1.61, 95%CI: 1.06 ~ 2.43; quartile 4: OR = 1.49, 95%CI: 1.06 ~ 2.10; *p* for trend = 0.011), 2-Nap (quartile 3: OR = 1.54, 95%CI: 1.10 ~ 2.15; quartile 4: OR = 1.46, 95%CI: 1.03 ~ 2.07; *p* for trend = 0.013), 1-Phe (quartile 3: OR = 1.59, 95%CI: 1.05 ~ 2.42; quartile 4: OR = 1.83, 95%CI: 1.07 ~ 3.15; *p* for trend = 0.015), 1-Pyr (quartile 4: OR = 1.65, 95%CI: 1.01 ~ 2.71; *p* for trend = 0.027), and 9-Flu (quartile 3: OR = 1.61, 95%CI: 1.10 ~ 2.35; quartile 4: OR = 1.72, 95%CI: 1.06 ~ 2.80; *p* for trend = 0.030) were significantly associated with increased odds of experiencing daytime sleepiness.

Correlation of urinary PAH monomers

Figure S1 presents the Pearson correlation coefficients of log-transformed urinary PAH monomers. The results indicated that nine urinary PAH monomers were significantly correlated with one another, with correlation coefficients ranging from 0.35 to 0.96 (all *p* values < 0.05). We further constructed a latent variable, consisting of the nine urinary metabolites, to represent PAH exposure. The standardized factor loadings of nine metabolites on the latent construct ranged from 0.58 and 0.98 (Fig. S2).

Associations between urinary PAH exposure and sleep-related disorders

The results of SEM showed significant association of urinary PAH exposure with long sleep-latency (β = 0.054, *p* = 0.035), but not with short sleep-latency (β = 0.018, *p* = 0.468) (Table 4**).** Urinary PAH exposure was also significantly positively associated with obstructive sleep apnea (β = 0.071, *p* = 0.002), as well as sleep problems (β = 0.089, *p* < 0.001) and daytime sleepiness (β = 0.066, *p* = 0.003).

Mediating role of CRP and WBC in the associations between urinary PAH metabolites and sleep-related disorders

Figure 2 presents the mediating effect of log-transformed white blood cell counts (logWBC) on the associations of PAH exposure with sleep-related disorders. The results suggested that logWBC mediated the association between PAH exposure and sleep problems (Indirect effect = 0.009, 95%CI: 0.002 ~ 0.017), as well as daytime sleepiness (Indirect effect = 0.011, 95%CI: 0.005 ~ 0.019). The proportion of the mediating effect explained by logWBC was 10.8% and 15.7% respectively. The mediating effects of logWBC on the associations between PAH exposure and long sleep-onset latency, as well as obstructive sleep apnea, did not reach statistical significance. Detailed estimates are presented in Table S1. The findings also suggested that the mediating effects of logCRP on the association between PAH exposure and the four sleep-related disorders were not statistically significant (Table S2).

Sensitivity analysis

To examine the robustness of our findings, we conducted weighted quantile sum (WQS) regression analyses to evaluate the association between PAH mixtures and sleep-related outcomes. The WQS index

was constrained in the positive direction, under the assumption that higher PAH exposure would be associated with increased odds of adverse sleep outcomes (Tables S3 and S4). Consistent with the results from SEM, the WQS index was significantly associated with increased odds of long sleep-onset latency (OR = 1.18, 95% CI: 1.01 ~ 1.36), obstructive sleep apnea (OR = 1.13, 95% CI: 1.00 ~ 1.27), sleep problems (OR = 1.17, 95% CI: 1.03 ~ 1.33), and daytime sleepiness (OR = 1.14, 95% CI: 1.01 ~ 1.30), while no significant association was found for short sleep-onset latency (OR = 1.09, 95% CI: 0.94 ~ 1.26).

Among the individual PAH metabolites, 1-Nap and 1-Phe were primary contributors to the WQS index for several outcomes. Specifically, 1-Nap accounted for 49.4% of the total weight for long sleep-onset latency and 69.2% for daytime sleepiness, while 1-Phe was the dominant contributor for sleep problems (43.5%) and obstructive sleep apnea (45.9%).

These results support the robustness of the main analysis and further highlight the potential role of specific PAH compounds—particularly 1-Nap and 1-Phe—in sleep disturbances.

Discussion

This study explored the associations between urinary PAH metabolites and various sleep-related disorders, including sleep-onset latency, sleep problems, obstructive sleep apnea, and daytime sleepiness, in the U.S. general population using a nationally-representative sample. In addition, the present study also examined the potential mediating role of systemic inflammatory markers, including C-reactive protein and white blood cell counts, in the relationship between PAH exposure and sleep-related disorders.

Our findings suggested that both individual urinary PAH metabolites and the latent PAH exposure variables were associated with an increased risk of multiple sleep-related outcomes, including long sleep-onset latency, obstructive sleep apnea, sleep problems, and daytime sleepiness, even after adjusting for a comprehensive set of covariates, which expanded researches on environmental exposure and sleep disorders. The WQS regression confirmed the robustness of the findings obtained from SEM, supporting the observed associations between PAH exposure and sleep outcomes. From the perspective of the sleep cycle, the findings revealed that the effects of PAH exposure on sleep may span the entire sleep process [29]. Specifically, in the early stages of sleep, individuals with high levels of PAH exposure were more likely to experience longer sleep latency, and during the middle of sleep cycle, participants with high levels of PAH exposure reported more sleep disturbance symptoms (e.g. insomnia and snoring). In addition, PAHs exposure was also associated with daytime dysfunction (i.e. daytime sleepiness).

The mechanisms linking PAH exposure and sleep disorders were not fully understood and might have the following aspects. First, PAHs may affect the biochemistry of the central nervous system, leading to altered neurochemical expression and dysregulation. PAHs have been considered neurotoxic compounds [30]. Evidence from animal studies has shown that PAHs impair learning and memory, and reduce neurotransmitter levels and brain metabolism in rats [31, 32]. Similar findings have been observed in population-based studies, which reported associations between PAH exposure and structural abnormalities in the brain, as well as reductions in neurotransmitters and cognitive function [33]. Thus, it is feasible to consider that effect of PAHs on sleep disorders might be partly caused by changing the biochemical functions of the central nervous system and further affecting the sleep–wake cycle of the central nervous system.

The effects of PAHs on the physiology of the respiratory system may offer another explanation for these associations. Studies have suggested that PAH exposure can lead to respiratory and lung damage [34, 35], inclding mucosal inflammation or edema, which may increased the restriction and obstruction of normal airflow, elevate the risk of apnea and hypoxia, and ultimately leading to respiratory disturbances and reduced sleep quality [29]. Notably, inflammation might be a crucial part of understanding the physiological processes of PAHs-related sleep disturbances. On the one hand, systemic inflammation might be one of the underlying mechanisms of PAHs exposure-induced neurodegeneration. Inflammatory responses triggered caused by PAH exposure can activate microglial cells in the brain , leading to neuroinflammation and subsequent neurodegeneration [36, 37]. On the other hand, inflammation was one of the early physiological responses following PAH exposure in the lungs, and plays a significant role in the process of PAH-induced pulmonary injury [38–40].

To understand the underlying mechanism of PAH exposure and sleep disturbance, we constructed a mediation analysis model of inflammation in the associations of PAHs with sleep disorders. The results showed that inflammatory markers, specifically white blood cell counts, mediated the relationship between PAH exposure and daytime sleepiness, as well as sleep problems,

Table 3 Logistic regressions for sleep outcomes for adult participants in NHANES 2005–2008, odds ratios (ORs) and 95% confidence intervals (CIs)

Variable	Obstructive sleep apnea		Sleep problems		Daytime sleepiness	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
1-Nap						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.14 (0.80, 1.63)	0.415	0.82 (0.52, 1.29)	0.343	1.16 (0.76, 1.76)	0.445
Quantile 3	1.16 (0.81, 1.65)	0.367	0.92 (0.60, 1.41)	0.683	1.61 (1.06, 2.43)	0.030
Quantile 4	1.14 (0.71, 1.83)	0.553	0.84 (0.54, 1.31)	0.402	1.49 (1.06, 2.10)	0.028
p for trend	0.569		0.516		0.011	
2-Nap						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.19 (0.81, 1.75)	0.327	1.18 (0.88, 1.58)	0.225	1.19 (0.78, 1.81)	0.383
Quantile 3	1.34 (0.96, 1.87)	0.080	1.30 (1.00, 1.68)	0.049	1.54 (1.10, 2.15)	0.018
Quantile 4	1.39 (0.88, 2.19)	0.135	1.31 (0.91, 1.87)	0.130	1.46 (1.03, 2.07)	0.036
p for trend	0.096		0.102		0.013	
3-Flu						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.60 (1.14, 2.23)	0.012	1.08 (0.87, 1.35)	0.456	1.12 (0.72, 1.75)	0.567
Quantile 3	1.66 (1.25, 2.19)	0.003	0.96 (0.68, 1.36)	0.798	1.25 (0.80, 1.96)	0.283
Quantile 4	1.88 (1.19, 2.97)	0.012	1.15 (0.81, 1.62)	0.384	1.38 (0.86, 2.22)	0.161
p for trend	0.019		0.595		0.148	
2-Flu						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.55 (1.13, 2.12)	0.012	1.14 (0.87, 1.51)	0.303	1.39 (0.96, 2.00)	0.073
Quantile 3	1.74 (1.23, 2.48)	0.006	1.08 (0.77, 1.52)	0.616	1.43 (0.89, 2.31)	0.123
Quantile 4	1.80 (1.08, 3.01)	0.029	1.23 (0.84, 1.81)	0.250	1.44 (0.97, 2.15)	0.069
p for trend	0.029		0.333		0.107	
3-Phe						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.14 (0.81, 1.61)	0.402	0.88 (0.60, 1.30)	0.478	1.01 (0.64, 1.60)	0.954
Quantile 3	1.51 (1.06, 2.14)	0.027	0.88 (0.60, 1.29)	0.470	1.08 (0.73, 1.59)	0.663
Quantile 4	1.76 (1.14, 2.71)	0.016	0.96 (0.65, 1.42)	0.833	1.49 (0.84, 2.65)	0.149
p for trend	0.009		0.903		0.084	
1-Phe						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.21 (0.85, 1.74)	0.258	1.11 (0.75, 1.65)	0.564	1.15 (0.76, 1.73)	0.460
Quantile 3	1.29 (0.86, 1.94)	0.195	1.27 (0.88, 1.85)	0.173	1.59 (1.05, 2.42)	0.033
Quantile 4	1.65 (1.06, 2.57)	0.030	1.40 (0.87, 2.26)	0.146	1.83 (1.07, 3.15)	0.031
p for trend	0.025		0.077		0.015	
2-Phe						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.20 (0.87, 1.66)	0.235	0.90 (0.60, 1.36)	0.593	1.05 (0.69, 1.62)	0.789
Quantile 3	1.23 (0.82, 1.83)	0.278	1.04 (0.70, 1.56)	0.820	1.20 (0.80, 1.81)	0.342
Quantile 4	1.55 (0.93, 2.60)	0.085	1.08 (0.69, 1.69)	0.719	1.44 (0.85, 2.45)	0.153
p for trend	0.095		0.493		0.115	
1-Pyr						
Quantile 1	[Ref]		[Ref]		[Ref]	
Quantile 2	1.00 (0.64, 1.56)	0.986	0.94 (0.66, 1.32)	0.676	1.01 (0.72, 1.44)	0.938
Quantile 3	1.26 (0.88, 1.81)	0.184	1.11 (0.76, 1.62)	0.549	1.30 (0.95, 1.76)	0.089
Quantile 4	1.36 (0.83, 2.24)	0.189	1.07 (0.72, 1.60)	0.706	1.65 (1.01, 2.71)	0.047
p for trend	0.062		0.511		0.027	

Table 3 (continued)

Variable	Obstructive sleep apnea		Sleep problems		Daytime sleepiness	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
9-Flu						
Quantile 1	[Ref]	-	[Ref]	-	[Ref]	-
Quantile 2	1.19 (0.81, 1.76)	0.332	0.77 (0.55, 1.08)	0.111	1.33 (0.92, 1.90)	0.111
Quantile 3	1.45 (0.92, 2.27)	0.098	1.34 (0.91, 1.97)	0.125	1.61 (1.10, 2.35)	0.020
Quantile 4	1.83 (1.04, 3.21)	0.039	1.12 (0.74, 1.69)	0.552	1.72 (1.06, 2.80)	0.032
p for trend	0.025		0.113		0.030	

All model adjusted for age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and urinary creatinine. OR (95%CI) means odds ratio and 95% confidence interval; Ref = Reference group

but this mediating effect did not reach statistical significance for long sleep-onset latency and obstructive sleep apnea. Available research evidence suggests that alterations in sleep depth and sleep architecture may be the pathway to inflammation-induced sleep disorders [41–43]. Studies have shown that increased levels of circulating proinflammatory factor IL-6 during the inflammation process correlate with increased amount and percentage of rapid eye movement sleep [44], as well as decreases in slow wave sleep (SWS) [45, 46], which suggests reduced sleep depth and increased likelihood of awakening. Moreover, the findings based on population studies suggested that markers of inflammation such as CRP, WBC, and proinflammatory cytokines were associated with fatigue or reduced vitality [47, 48]. Further studies have suggested that changes in sleep architecture, such as the relative loss of SWS, might be a pathway for cellular inflammation leading to daytime fatigue [43]. Poor sleep quality also slowed down the energy recovery process of the body, leading to excessive sleepiness and fatigue.

Table 4 The associations between urinary PAH exposure and sleep-related disorders in U.S. adults: Structural equation model results

Outcomes	n	β	C.R	*P* value
Short sleep-onset latency	2,024	0.018	0.725	0.468
Long sleep-onset latency	1,833	0.054	2.105	0.035
Obstructive sleep apnea	2,220	0.071	3.174	0.002
Sleep problems	2,520	0.089	4.042	< 0.001
Daytime sleepiness	2,515	0.066	2.996	0.003

β represents the standardized regression coefficient of the latent PAH exposure variable on sleep-related disorders. C.R. = Critical Ratio. Fit indexes: Short sleep-onset latency: CFI = 0.94, NFI = 0.93, RMSEA = 0.08, SRMR = 0.04; Long sleep-onset latency: CFI = 0.94, NFI = 0.93, RMSEA = 0.08, SRMR = 0.05; Obstructive sleep apnea: CFI = 0.94, NFI = 0.93, RMSEA = 0.08, SRMR = 0.05; Sleep problems: CFI = 0.94, NFI = 0.93, RMSEA = 0.08, SRMR = 0.04; Daytime sleepiness: CFI = 0.94, NFI = 0.93, RMSEA = 0.08, SRMR = 0.04. All models were adjusted for age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and urinary creatinine

Overall, this evidence supports the findings of this study that inflammation may be one pathway through which PAHs contribute to sleep problems such as insomnia, and daytime sleepiness, providing considerable value for understanding the underlying mechanisms of PAH-induced sleep disturbances.

The findings from the present study also suggested that the inflammatory process was also reported to be associated with increased OSA risk [49], while the mediating effect of inflammation was relatively low and did not reach statistical significance, which to some extent indicates that the role of inflammation in PAH-induced OSA may be limited. In addition, existing evidence also suggested that OSA is associated with upper airway inflammation-related outcomes, such as upper airway collapse, airway edema, or obstruction, leading to stenosis of the airway and reduced or ceased airflow [50, 51], rather than inflammation itself. However, information on airway inflammation or anatomical structure in NHANES data were not assessed and measured. More extensive studies should be conducted to validate these results. Overall, the differential mediation findings across sleep outcomes may reflect underlying pathophysiological differences. Daytime sleepiness and sleep problems are more directly influenced by systemic inflammation and general health status, whereas obstructive sleep apnea is largely structural or anatomical in origin. Similarly, short or long sleep-onset latency may be affected by neurobehavioral or psychological factors less directly linked to inflammation. These differences may explain the limited mediating role of inflammation in OSA and sleep latency outcomes.

Several limitations of this study should be acknowledged when interpreting the findings. First, the cross-sectional design of NHANES limits the ability to establish causal relationships between PAH exposure, inflammatory markers, and sleep-related disorders. Future research should adopt longitudinal study designs to better clarify the temporal and causal pathways linking environmental exposures to sleep disturbances. Second,

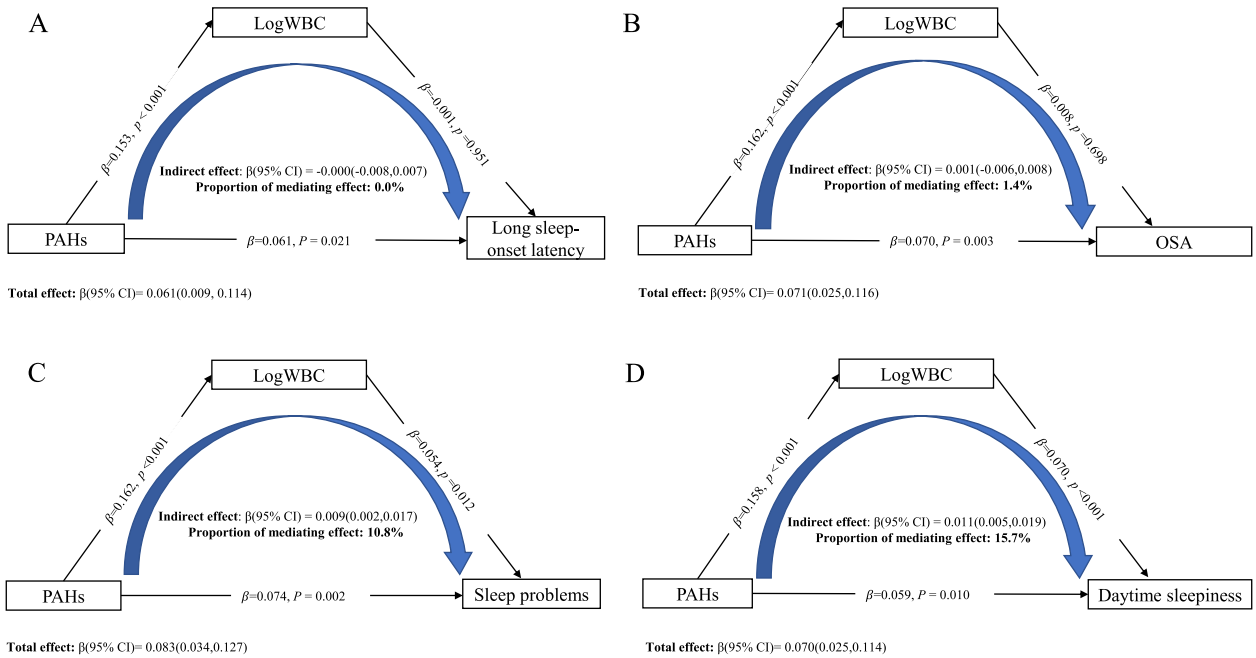

Fig. 2 Mediation effect of log-transformed white blood cell counts (logWBC) on the associations between PAH exposure and sleep-related disorders. (**A**) Long sleep-onset latency ($n = 1,743$), (**B**) Obstructive sleep apnea ($n = 2,122$), (**C**) Sleep problems ($n = 2,402$) and (**D**) Daytime sleepiness ($n = 2,397$). Fit indexes: (**A**): CFI = 0.93, NFI = 0.92, RMSEA = 0.08, SRMR = 0.05; (**B**): CFI = 0.93, NFI = 0.92, RMSEA = 0.08, SRMR = 0.05; (C): CFI = 0.93, NFI = 0.92, RMSEA = 0.08, SRMR = 0.05; (**D**): CFI = 0.93, NFI = 0.92, RMSEA = 0.08, SRMR = 0.05. β represents the standardized path coefficient from the predictor to the outcomer. All models were adjusted for age, gender, race/ethnicity, marital status, education level, poverty income ratio, BMI, alcohol use, cigarette use, diabetes, hypertension, cardiovascular diseases, work status, and urinary creatinine

urinary PAH metabolites were assessed using a single spot urine sample, which reflects only recent exposure and may not accurately capture long-term or cumulative PAHs burden. Repeated biomonitoring or the use of more stable biological matrices (e.g., hair, nails) could improve the assessment of long-term exposure in future studies. Third, the sleep-related outcomes—including sleep-onset latency, sleep problems, obstructive sleep apnea, and daytime sleepiness—were based on self-reported data, which may introduce recall bias or misclassification. Incorporating objective sleep assessments, such as actigraphy or polysomnography, alongside self-reported measures in future research, would enhance the validity of sleep outcome measurements. Finally, although we adjusted for a wide range of demographic, lifestyle, and health-related confounders, the NHANES dataset lacks data on other relevant environmental exposures, such as air pollution, sleep-related noise, and light pollution. These unmeasured exposures could not be adjusted for and may have confounded the observed associations. Future research should aim to incorporate a broader spectrum of environmental exposures to more comprehensively evaluate the combined effects of exposure mixtures on sleep and inflammation.

Conclusions

In conclusion, our study demonstrated that urinary PAH exposure was associated with an increased risk of sleep-related outcomes, including long sleep-onset latency, obstructive sleep apnea, sleep problems, and daytime sleepiness. Besides, inflammatory markers that white blood cell counts was found to mediated the relationship between PAH exposure and both daytime sleepiness and sleep problems, providing a significant value for understanding the underlying mechanisms linking PAH exposure to sleep-related disturbances.

Abbreviations

PAHs	Polycyclic aromatic hydrocarbons
1-Nap	1-Hydroxynaphthalene
2-Nap	2-Hydroxynaphthalene
1-Phe	1-Hydroxyphenanthrene
2-Phe	2-Hydroxyphenanthrene
3-Phe	3-Hydroxyphenanthrene
2-Flu	2-Hydroxyfluorene
3-Flu	3-Hydroxyfluorene
9-Flu	9-Hydroxyfluorene
1-Pyr	1-Hydroxypyrene
OSA	Obstructive sleep apnea
CRP	C-reactive protein
WBC	White blood cell counts
SEM	Structural Equation Modelling
CFI	Comparative fit index
NFI	Normed Fit Index
SRMSR	Standardized Root Mean Square Residual
RMSEA	Root mean square error approximation

OR	Odds ratio
CI	Confidence interval
NHANES	National Health and Nutrition Examination Survey

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Bin Yang: Conceptualization, Writing—original draft. Mengqing Yan: Writing—original draft, Data curation. Zhiguang Gu: Resources, Data curation. Zeming Niu: Validation, Writing-review & editing. Jing Sun: Validation, Writing-review & editing. Jingwen Guo: Visualization, Writing-review & editing. Qi Wang: Conceptualization, Methodology. Yongli Yang: Formal analysis, Methodology, Supervision. Wei Wang: Conceptualization, Methodology, Financial support. All authors read and approved the final manuscript.

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Data availability
All data used in this study could be obtained from the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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