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RESEARCH ARTICLE

Urinary polycyclic aromatic hydrocarbon metabolites and depression: a cross-sectional study of the National Health and Nutrition Examination Survey 2005–2016

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Abstract

Background The adverse effects of polycyclic aromatic hydrocarbon (PAHs), a group of common environmental pollutants, on mental health are unclear. This study is developed to evaluate the potential association of urinary PAH metabolites with depression in US adults.

Methods Measurement of 8 urinary PAH metabolites and assessment of depression were available for 9625 adults in the National Health and Nutritional Examination Survey 2005–2016. Multiple logistic regression models and weighted quantile sum (WQS) regression models were applied to evaluate the association between urinary PAH metabolites and depression.

Results Among 9625 individuals with a weighted geometric mean age of 42.63 years, 801 participants suffered from depression. Significant positive dose–response relationships were observed between specific urinary PAH metabolites and the risk of depression after adjusting for potential confounders. Urinary 1-hydroxynaphthalene was positively and dose-dependently associated with the risk of depression among total participants (odds ratio: 1.188; 95% confidence interval: 1.096–1.288). In addition, each 1-unit increase of ln-transformed urinary 1-hydroxynaphthalene, 2-hydroxynaphthalene, 3-hydroxyfluorene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 2&3-hydroxyphenanthrene, 1-hydroxypyrene, and total PAH metabolites was associated with a 23.3%, 32.6%, 23.3%, 29.4%, 30.8%, 22.8%, 29.4%, and 31.7% increment in the risk of depression in smokers, respectively (all P and $P_{trend} < 0.05$). Of note, the positive WQS index was also significantly associated with the increased risk of depression in smokers (1.122, 1.059–1.188).

Conclusion Exposure to PAHs may elevate the risk of depression among US adults. More studies are warranted to investigate the underlying mechanism by which PAHs induce the development of depression.

Keywords Polycyclic aromatic hydrocarbons · Depression · Weighted quantile sum regression

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Introduction

Polycyclic aromatic hydrocarbons (PAHs) which refer to a group of aromatic hydrocarbons containing two or more benzene rings are a kind of ubiquitous environmental contaminants formed from incomplete combustion of organic materials. Accumulating evidence has explored the adverse effects of PAH exposure on health, including increased risk of cardiovascular disease and diabetes, alteration of thyroid function, reproductive function, and lung function, and even resulted in cancers such as lung cancer (Cao et al. 2020b; Kelishadi et al. 2018; Kim et al. 2013; Yang et al. 2017; Zhang et al. 2021a; Zhou et al. 2016). Of note, recent studies revealed that PAH exposure was associated with neurobehavioral disorders. A birth cohort study of 258 children yielded that maternal

exposure to PAHs was associated with adverse neurobehavioral development outcomes in Taiyuan, China (Cao et al. 2020c). And the New York City cohort study including 253 mother–child pairs also suggested that PAH exposure during pregnancy might result in an increased risk of depression symptoms in children (Perera et al. 2012). In addition, a recent study revealed a positive association between urine PAHs and depressive symptoms in females (Zhang et al. 2021b). However, the association between PAH exposure and neurobehavioral disorders such as depression in adults remains largely unknown.

Depression, a common mental disorder characterized by persistent low mood and a range of associated emotional, cognitive, physical, and behavioral symptoms, is regarded as a highly prevalent chronic illness accompanied by the disorder of brain structure and function (National Collaborating Centre for Mental Health 2010). The World Health Organization announced that more than 264 million people suffered from depression worldwide in 2017 (WHO 2021). And in the USA, around 17.3 million adults aged 18 or older experienced depression in 2017, which represented 6.7% of all US adults (ADAA 2018). As the leading cause of disability among people ages 15–44 in 2017 in the USA (ADAA 2018), depression largely and negatively affects the quality of life, including reduced school performance, work efficiency, relationships with family and friends, and ability to participate in the community (Kessler and Bromet 2013; Stewart et al. 2003; WHO 2021). Besides, depression was closely related to physical health, such as cardiovascular disease and Parkinson's disease (Carney and Freedland 2017; Jeong et al. 2021). Therefore, the potential pathogenic factors for depression have received great attention. Except for common social and genetic risk factors, emerging evidence suggests that environmental pollutants are also positively associated with the development of depression (Braithwaite et al. 2019; Hao et al. 2021). Based on the neurobehavioral damage of PAH, it is reasonable to assume that this environmental pollutant may be related to depression.

Herein, we took 9625 adults from the US National Health and Nutrition Examination Survey (NHANES) from 2005 to 2016 as the research participants. Eight urinary PAH metabolites were determined for all participants to reflect internal levels of PAH exposure. Depression for the participants was assessed by specialists through the PHQ-9 scale. The objective of this present study was to evaluate the association between urinary PAH metabolites and the risk of depression among US adults.

Methods

Study populations

The study participants were originated from the continuous NHANES, which was started in 1999 and was conducted in every 2-year cycle with a complex, multistage, stratified, clustered probability design to represent US adults and to investigate the relationships between nutrition, living environment, habits, and health. Data on demographics, lifestyles, and health status were obtained by questionnaires, physical examinations, and laboratory tests. In the 6 consecutive cycles of the NHANES from 2005 to 2016, a total of 15,385 individuals with measurement of urinary PAH metabolites were included in this study. After excluding individuals without assessment of the 9-item Patient Health Questionnaire (PHQ-9) or aged < 18 years, 9625 participants were finally evaluated. The NHANES was reviewed and approved by the US Centers for Disease Control and Prevention National Center for Health Statistics Research Ethics Review Board, and all participants provided written informed consent.

Determination of urinary PAH metabolites

Urine specimens were collected and stored at − 70 °C until for determination of urinary PAH metabolites. Eight urinary concentrations of PAH metabolites including 1-hydroxynaphthalene (1-OHNa), 2-hydroxynaphthalene (2-OHNa), 2-hydroxyfluorene (2-OHFlu), 3-hydroxyfluorene (3-OHFlu), 1-hydroxyphenanthrene (1-OHPh), 2-hydroxyphenanthrene (2-OHPh), 3-hydroxyphenanthrene (3-OHPh), and 1-hydroxypyrene (1-OHP) were all measured in 6 cycles of the NHANES 2005–2016. And 2&3-OHPh was regarded as the sum of the concentrations of 2-OHPh and 3-OHPh as they were measured together in NHANES 2013–2014 and 2015–2016 (Table S1). The details of the method for urinary PAH metabolite determination were reported previously (Romanoff et al. 2006; Wang et al. 2017). Total PAH metabolites (∑OH-PAHs) were the sum of the concentrations of the above 8 PAH metabolites. The limits of detection (LOD) and detectable rate (≥ LOD) of each urinary PAH metabolite for each NHANES cycle are provided in Table S1. The concentrations of those samples below the LOD were replaced with the LOD divided by the square root of 2 (Romanoff et al. 2006; Wang et al. 2017). Valid urinary PAH metabolite concentrations were adjusted by levels of urinary creatinine (Cr) and expressed as micrograms/gram (μg/g) of Cr.

Assessment of depression

Depression was assessed by PHQ-9, which was widely used and regarded as a valid and utile tool for diagnosing

depression (Spitzer et al. 1999). The PHQ-9 evaluated the overall impairment of the symptoms through 9 symptom items. Each symptom item is scored by response categories: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day), resulting in a total score ranging from 0 to 27. According to previous studies (Hao et al. 2021; Spitzer et al. 1999), a total score of ≥ 10 was considered depression.

Covariates

Covariates were collected from questionnaires and physical examinations, which covered information on demographic (age, gender, race/ethnicity, education level, family income-poverty ratio (PIR), and marital status), lifestyles (smoking status, drinking status, and physical activity), general health condition, health insurance coverage, and body mass index (BMI, kg/m^2). The race/ethnicity included four types: Mexican American, non-Hispanic white, non-Hispanic black, and others. Education level was categorized as less than high school, high school or equivalent, and college or above. PIR was divided into three categories: 0–1, 1.1–3.0, > 3.0. Marital status was grouped as married/living with partner, and single/divorced/widowed. Individuals who smoked less than 100 cigarettes in life were regarded as non-smokers, others were regarded as smokers. Among smokers, those who smoked more than 100 cigarettes but were not smokers at the time of the survey were regarded as former smokers; otherwise, they were current smokers (Chen et al. 2019). Drinking status was divided into three groups: non-drinkers (0), low to moderate drinkers (less than 2 drinks/day), and heavy drinkers (more than 2 drinks/day). Individuals with vigorous or moderate activity over the past 30 days were defined as active physical activity. General health conditions and health insurance coverage were self-reported, and the former was classified into three categories: poor to fair, good, and very good to excellent.

Statistical analysis

Appropriate sample weights, strata, and cluster variables were used in the analyses to account for the complex, multistage sampling design in the NHANES (Statistics 2020). Categorical variables were expressed as number (weighted proportion) and compared by the Rao-Scott χ^2 test, while continuous variables were presented as weighted geometric mean (GM, standard error (SE)) and tested by analysis of variance or Kruskal–Wallis test. In addition, PAH metabolite concentrations were natural log (ln)-transformed due to skewed distributions. Spearman rank correlation was conducted to assess correlations between individual urinary PAH metabolites and ∑OH-PAHs. Further analyses were stratified by smoking status as smoking was one of the main sources of PAH exposure. We constructed multiple logistic regression models using the SURVEYLOGISTIC procedure to estimate the association between urinary PAH metabolites and depression in both continuous and categorical analyses with adjustment for confounders including gender, age, BMI, race, education level, marital status, PIR, smoking status, drinking status, physical activity, general health condition, and health insurance coverage. In addition, we performed stratified analyses and evaluated the effect modifications by selected characteristics (gender, age, BMI, education level, marital status, drinking status, and physical activity) in the associations of urinary PAH metabolites with depression.

Furthermore, weighted quantile sum (WQS) regression was used to assess the effect of PAH metabolites mixture on depression with R package "*gWQS*." In contrast to single chemical analysis, the WQS regression is a kind of typical mixed exposure statistical model, which can estimate the mixed effect of all exposure on the outcome and identify the contribution of each component with non-negligible weights (Carrico et al. 2015). Given the complex algorithm, sample weights, strata, and cluster variables did not adapt to the WQS regression models (Luo et al. 2020). According to the WHO recommendations (WHO 1996), we further performed sensitivity analyses of the association between PAHs and depression after excluding individuals with too dilute (Cr < 30 mg/dL) or too concentrated urine samples (Cr > 300 mg/dL). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.2 (R Core Team 2020) with a 2-sided $P < 0.05$ considered statistically significant.

Results

Basic characteristics

Table 1 presents the basic characteristics of 9625 participants categorized by sex. The weighted GM (SE) of age and BMI among total participants was 42.63 (0.31) years and 28.01 (0.10) kg/m^2, respectively. The numbers (weighted proportions) for males and females among total participants were 4817 (49.08) and 4808 (50.92), respectively. Males were more likely to be smokers and heavy drinkers (all $P < 0.05$). Among total participants, 801 participants (6.74%) developed depression. And the weighted proportion of depression in females was higher than that in males ($P < 0.05$).

Distribution of urinary PAH metabolites

The weighted GM (SE) of urinary ∑OH-PAHs was 9.16 (0.18) μg/g Cr among 9625 participants (Table 2). Among urinary individual PAH metabolites, 1-OHNa and 2-OHNa

Table 1 Basic characteristics of the participants in NHANES 2005–2016 according to sex ($n = 9625$)

Characteristic	Total participants	Male	Female	*P* value*
No. subjects	9625	4817 (49.08)	4808 (50.92)	
Age, years, (GM, SE)	42.63 (0.31)	41.88 (0.40)	43.35 (0.38)	< 0.001
BMI, kg/m^2, (GM, SE)	28.01 (0.10)	28.08 (0.11)	27.94 (0.13)	0.458
Race, *n* (%)				0.007
Mexican American	1589 (8.66)	782 (9.37)	807 (7.98)	
Non-Hispanic White	4101 (67.85)	2073 (67.92)	2028 (67.78)	
Non-Hispanic Black	2060 (11.22)	1052 (10.49)	1008 (11.92)	
Others	1875 (12.27)	910 (12.22)	965 (12.32)	
Education level, *n* (%)				0.027
Less than high school	2277 (16.02)	1180 (17.12)	1097 (14.97)	
High school or equivalent	2354 (23.25)	1199 (23.56)	1155 (22.95)	
College or above	4994 (60.73)	2438 (59.32)	2556 (62.08)	
Marital status, *n* (%)				< 0.001
Married/living with partner	5699 (63.32)	3114 (68.04)	2585 (58.77)	
Single/divorced/widowed	3926 (36.68)	1703 (31.96)	2223 (41.23)	
PIR, *n* (%)				< 0.001
0–1.0	2100 (14.47)	953 (12.85)	1147 (16.03)	
1.1–3.0	4113 (37.09)	2084 (36.88)	2029 (37.30)	
> 3.0	3412 (48.44)	1780 (50.27)	1632 (46.67)	
Smoking status, *n* (%)				< 0.001
Non-smokers	5240 (53.89)	2197 (47.85)	3043 (59.73)	
Former smokers	2440 (25.91)	1508 (30.35)	932 (21.62)	
Current smokers	1945 (20.20)	1112 (21.80)	833 (18.65)	
Drinking status, *n* (%)				< 0.001
Non-drinkers	2094 (16.97)	630 (10.26)	1464 (23.44)	
Low to moderate drinkers	2832 (30.16)	1254 (24.53)	1578 (35.58)	
Heavy drinkers	4699 (52.87)	2933 (65.21)	1766 (40.97)	
Physical activity, active, *n* (%)	4893 (56.94)	2579 (59.23)	2314 (54.74)	< 0.001
Health insurance coverage, covered, *n* (%)	7481 (81.83)	3628 (79.37)	3853 (84.20)	< 0.001
General health condition, *n* (%)				0.321
Very good to excellent	3533 (43.98)	1799 (43.58)	1734 (44.37)	
Good	3877 (39.03)	1963 (39.89)	1914 (38.20)	
Poor to fair	2215 (16.99)	1055 (16.53)	1160 (17.44)	
Depression, *n* (%)	801 (6.74)	300 (5.17)	501 (8.24)	< 0.001

GM geometric mean, *SE* standard error, *BMI* body mass index, *PIR* family income-poverty ratio

showed higher levels of concentrations, and the GMs (SE) were 2.32 (0.06) and 4.02 (0.16) μg/g Cr, respectively. Furthermore, the levels of urinary total PAH and eight individual PAH metabolites in smokers were significantly higher than those in non-smokers (all $P < 0.05$). Moreover, Figure S1 displays the correlations between total and individual urinary PAH metabolites. Urinary PAH metabolites were moderately to highly correlated with each other with Spearman correlation coefficients ranging from 0.31 to 0.92 (all $P < 0.05$).

Independent associations between urinary PAH metabolites and depression

Table 3 demonstrates the relationships between individuals and total urinary PAH metabolites and depression after adjusting for potential confounders. In the continuous analyses, each 1-unit increase in ln-transformed values of urinary 1-OHNa and ∑OH-PAHs was associated with an 18.8% (odds ratio (OR): 1.188; 95% confidence interval (CI): 1.096–1.288) and 22.3% (1.223, 1.087–1.376) increased risk of depression among total

Table 2 Weighted distribution of urinary polycyclic aromatic hydrocarbon metabolites ($n = 9625$)

	Urinary PAH metabolites concentrations, μg/g Cr				*P* value[a]
	GM (SE)	Percentile			
		P25	P50	P75	
1-OHNa					
Total	2.32 (0.06)	0.78	1.70	5.91	
Non-smokers	1.45 (0.04)	0.63	1.15	2.50	< 0.001
Smokers	4.02 (0.16)	1.16	3.90	12.51	
2-OHNa					
Total	4.47 (0.08)	2.16	4.16	9.18	
Non-smokers	3.43 (0.07)	1.85	3.20	5.92	< 0.001
Smokers	6.10 (0.14)	2.88	6.37	13.35	
3-OHFlu					
Total	0.11 (0.002)	0.05	0.08	0.22	
Non-smokers	0.07 (0.001)	0.04	0.06	0.10	< 0.001
Smokers	0.19 (0.01)	0.06	0.16	0.65	
2-OHFlu					
Total	0.27 (0.005)	0.13	0.20	0.49	
Non-smokers	0.18 (0.003)	0.11	0.16	0.25	< 0.001
Smokers	0.43 (0.01)	0.16	0.37	1.16	
1-OHPh					
Total	0.14 (0.002)	0.08	0.13	0.21	
Non-smokers	0.12 (0.002)	0.07	0.11	0.17	< 0.001
Smokers	0.16 (0.002)	0.10	0.15	0.25	
2&3-OHPh					
Total	0.15 (0.002)	0.09	0.14	0.23	
Non-smokers	0.12 (0.002)	0.08	0.12	0.18	< 0.001
Smokers	0.19 (0.003)	0.10	0.18	0.32	
1-OHP					
Total	0.12 (0.002)	0.07	0.12	0.21	
Non-smokers	0.10 (0.002)	0.06	0.10	0.16	< 0.001
Smokers	0.15 (0.003)	0.08	0.15	0.29	
∑OH-PAHs					
Total	9.16 (0.18)	4.25	7.43	16.82	
Non-smokers	6.70 (0.13)	3.64	5.87	10.12	< 0.001
Smokers	13.21 (0.39)	5.44	11.91	29.49	

[a]*P* value was tested log-transformed urinary PAH metabolite between non-smokers and smokers *Abbreviation*: *PAH* polycyclic aromatic hydrocarbon, *1-OHNa* 1-hydroxynaphthalene, *2-OHNa* 2-hydroxynaphthalene, *2-OHFlu* 2-hydroxyfluorene, *3-OHFlu* 3-hydroxyfluorene, *1-OHPh* 1-hydroxyphenanthrene, *2&3-OHPh* 2-hydroxyphenanthrene and 3-hydroxyphenanthrene, *1-OHP* 1-hydroxypyrene, *∑OH-PAHs* total PAHs metabolites, *GM* geometric mean, *SE* standard error

participants. The categorical analysis also showed a positive dose–response relationship between 1-OHNa and depression ($P_{trend} < 0.05$). Compared with individuals with the lowest quartile of 1-OHNa, those with the third (OR: 1.702, 95% CI: 1.087–2.664) and fourth quartiles (2.164, 1.470–3.187) showed an increased risk of depression. No significant relationships were observed between other PAH metabolites and depression among the total participants although an increased risk of depression without significant difference was found for urinary 3-OHFlu, 2-OHFlu, 1-OHPh, and 1-OHP.

Positive and significant dose–response relationships were observed between all urinary PAH metabolites and depression in smokers (all $P_{trend} < 0.05$). And each 1-unit increase of ln-transformed urinary 1-OHNa, 2-OHNa, 3-OHFlu, 2-OHFlu, 1-OHPh, 2&3-OHPh, and 1-OHP was related with a 23.3%, 32.6%, 23.3%, 29.4%, 30.8%, 22.8%, 29.4%, and 31.7% increase in the risk of depression among smokers, respectively (all $P < 0.05$), whereas only 1-OHNa was significantly and dose-dependently associated with depression in non-smokers ($P_{trend} < 0.05$), and the risk of depression increased 23.2%, corresponding to each 1-unit increase in ln-transformed values of 1-OHNa. We found that smoking status significantly modified the effect of 2-OHNa, 1-OHPh, and 1-OHP on the risk of depression (all *P* value for effect modification < 0.05, Table 3). Results from sensitive analyses were similar to the above findings (Table S2).

The associations of urinary ∑OH-PAHs and 1-OHNa with depression stratified by BMI, education level, marital status, drinking status, and physical activity are presented in Table S3. The positive associations of urinary PAH metabolites with depression were more pronounced among females, individuals aged > 45 years, individuals with BMI > 25 kg/m^2, individuals with higher education level (college or above), individuals married/living with partner, drinkers, and individuals with active physical activity. However, the above characteristics were not found to have significant effect modifications on the associations between urinary 1-OHNa and ∑OH-PAHs and depression (Table S3).

WQS analysis of the association between urinary PAH metabolites and depression

The relationship between urinary PAH metabolite mixture and depression evaluated by WQS is shown in Table 4. The WQS index was significantly associated with an elevated risk of depression in smokers (OR: 1.122; 95% CI: 1.059–1.188), and was marginally associated with an increased risk of depression in non-smokers (1.063, 0.998–1.133). Moreover, 2-OHNa had the largest contribution in smokers (Fig. 1A and Table S4), accounting for 60.15% of PAH exposure mixed effects, while the contributions of other urinary PAH metabolites were as follows: 1-OHNa (19.68%), 2-OHFlu (13.56%), 1-OHPh (2.52%), 3-OHFlu (2.23%), 1-OHP (1.23%), and 2&3-OHPh (0.62%). And 1-OHNa (66.98%) and 2-OHFlu (22.46%) were the highest contributors in the association between PAH metabolite mixture and depression

Table 3 Associations between urinary polycyclic aromatic hydrocarbon metabolite and depression in US adults ($n = 9625$)

Urinary PAH metabolites	OR (95% CI) by continuous log-transformed urinary PAH metabolite	OR (95% CI) by quartile of urinary PAH metabolite				*P* trend[a]	*P* value for effect modification
		Q1	Q2	Q3	Q4		
1-OHNa							
Total	**1.188 (1.096, 1.288)**	1 (ref.)	1.004 (0.724, 1.392)	1.233 (0.871, 1.745)	**1.465 (1.049, 2.047)**	**0.018**	
Non-smokers	**1.232 (1.077, 1.408)**	1 (ref.)	1.132 (0.736, 1.741)	1.452 (0.877, 2.404)	**1.928 (1.252, 2.970)**	**0.002**	0.993
Smokers	**1.233 (1.131, 1.343)**	1 (ref.)	0.978 (0.615, 1.556)	**1.702 (1.087, 2.664)**	**2.164 (1.470, 3.187)**	**< 0.001**	
2-OHNa							
Total	1.031 (0.899, 1.181)	1 (ref.)	0.793 (0.585, 1.076)	0.952 (0.667, 1.359)	0.921 (0.655, 1.295)	0.915	
Non-smokers	0.978 (0.779, 1.228)	1 (ref.)	0.992 (0.605, 1.627)	1.004 (0.639, 1.577)	0.835 (0.500, 1.396)	0.508	**0.002**
Smokers	**1.326 (1.153, 1.525)**	1 (ref.)	1.073 (0.690, 1.670)	1.471 (0.935, 2.314)	**2.135 (1.461, 3.120)**	**< 0.001**	
3-OHFlu							
Total	1.079 (0.954, 1.220)	1 (ref.)	0.937 (0.683, 1.287)	0.885 (0.630, 1.244)	1.258 (0.878, 1.804)	0.451	
Non-smokers	1.182 (0.960, 1.455)	1 (ref.)	0.932 (0.593, 1.465)	1.127 (0.724, 1.754)	1.149 (0.755, 1.750)	0.370	0.436
Smokers	**1.233 (1.102, 1.379)**	1 (ref.)	0.648 (0.409, 1.025)	1.433 (0.952, 2.158)	**1.633 (1.104, 2.415)**	**0.001**	
2-OHFlu							
Total	1.122 (0.978, 1.287)	1 (ref.)	0.910 (0.677, 1.222)	0.864 (0.622, 1.202)	1.262 (0.880, 1.808)	0.377	
Non-smokers	1.227 (0.981, 1.534)	1 (ref.)	0.774 (0.485, 1.235)	1.093 (0.731, 1.634)	1.042 (0.702, 1.548)	0.481	0.411
Smokers	**1.294 (1.144, 1.463)**	1 (ref.)	1.196 (0.743, 1.927)	**1.678 (1.130, 2.490)**	**2.353 (1.563, 3.541)**	**< 0.001**	
1-OHPh							
Total	1.076 (0.931, 1.244)	1 (ref.)	1.099 (0.795, 1.518)	1.068 (0.787, 1.448)	1.114 (0.826, 1.503)	0.574	
Non-smokers	0.981 (0.765, 1.259)	1 (ref.)	1.255 (0.743, 2.119)	0.944 (0.592, 1.504)	0.974 (0.612, 1.549)	0.523	**0.028**
Smokers	**1.308 (1.127, 1.518)**	1 (ref.)	0.861 (0.565, 1.312)	1.313 (0.856, 2.013)	**1.560 (1.052, 2.315)**	**0.002**	
2&3-OHPh							
Total	1.035 (0.894, 1.198)	1 (ref.)	0.760 (0.539, 1.073)	0.819 (0.610, 1.099)	0.970 (0.726, 1.295)	0.862	
Non-smokers	1.079 (0.833, 1.398)	1 (ref.)	0.640 (0.428, 0.958)	0.837 (0.507, 1.384)	0.932 (0.618, 1.406)	0.916	0.260
Smokers	**1.228 (1.052, 1.432)**	1 (ref.)	0.889 (0.602, 1.311)	**1.578 (1.089, 2.288)**	**1.557 (1.067, 2.271)**	**0.002**	
1-OHP							
Total	1.091 (0.956, 1.246)	1 (ref.)	0.823 (0.612, 1.107)	0.905 (0.677, 1.210)	1.147 (0.851, 1.546)	0.198	
Non-smokers	1.085 (0.863, 1.363)	1 (ref.)	0.835 (0.504, 1.385)	1.161 (0.750, 1.796)	1.017 (0.655, 1.579)	0.578	**0.034**
Smokers	**1.294 (1.123, 1.491)**	1 (ref.)	0.941 (0.582, 1.521)	1.426 (0.983, 2.069)	**1.999 (1.313, 3.043)**	**< 0.001**	
∑OH-PAHs							
Total	**1.223 (1.087, 1.376)**	1 (ref.)	0.943 (0.676, 1.316)	0.914 (0.643, 1.301)	1.244 (0.876, 1.768)	0.231	
Non-smokers	**1.256 (1.021, 1.544)**	1 (ref.)	0.911 (0.589, 1.407)	1.236 (0.807, 1.893)	1.247 (0.791, 1.968)	0.198	0.573
Smokers	**1.317 (1.177, 1.473)**	1 (ref.)	0.665 (0.410, 1.076)	1.308 (0.795, 2.152)	**1.893 (1.294, 2.769)**	**< 0.001**	

Adjusted for gender, age, BMI, race, education level, marital status, PIR, smoking status, drinking status, physical activity, general health condition, and health insurance coverage in weighted logistic regression models

Abbreviation: *PAH* polycyclic aromatic hydrocarbon, *1-OHNa* 1-hydroxynaphthalene, *2-OHNa* 2-hydroxynaphthalene, *2-OHFlu* 2-hydroxyfluorene, *3-OHFlu* 3-hydroxyfluorene, *1-OHPh* 1-hydroxyphenanthrene, *2&3-OHPh* 2-hydroxyphenanthrene and 3-hydroxyphenanthrene, *1-OHP* 1-hydroxypyrene, *∑OH-PAHs* total PAHs metabolites, *BMI* body mass index, *PIR* family income-poverty ratio, *OR* odds ratio, *CI* confidence interval

[a]*P* trend was tested by entering urinary PAH metabolites categories as continuous variables in models

in nonsmokers (Fig. 1B and Table S4). Sensitivity analyses showed similar mixed effects of PAH exposure on the risk of depression (Table S5).

Discussion

To our knowledge, few studies have addressed the association between PAH exposure and the risk of depression although published studies have reported a series of adverse health effects of PAH exposure (Kim et al. 2013). Toxicology studies have discovered that exposure to PAHs during

Table 4 The associations between urinary polycyclic aromatic hydrocarbon metabolite mixture and depression in the WQS regression ($n = 9625$)

	OR	95% CI	*P* value
Total participants	0.989	0.939–1.042	0.681
Non-smokers	1.063	0.998–1.133	0.059
Smokers	1.122	1.059–1.188	**< 0.001**

Adjusted for gender, age, BMI, race, education level, marital status, PIR, smoking status, drinking status, physical activity, general health condition, and health insurance coverage

OR odds ratio, *CI* confidence interval

the prenatal and neonatal periods could result in neurodevelopmental and behavioral effects such as depression-like symptoms (Peiffer et al. 2013; Yokota et al. 2009). And the Columbia Center for Children's Environmental Health longitudinal cohort study indicated that exposure to PAHs was positively associated with the symptom of depression among children aged 6–7 years (Perera et al. 2012). Furthermore, previous studies reported that cigarette smoking, one of the main sources for PAH exposure (Cao et al. 2020a), was associated with increased risk of depression (Fluharty et al. 2017). However, the direct evidence for PAH exposure inducing the development of depression in adults was limited. In this study, we found significantly positive associations of urinary PAH metabolites with the risk of depression among US adults. Both multiple logistic regression and WQS regression revealed that PAH exposure might increase the risk of depression, especially in smokers. Thus, reducing exposure to PAHs as well as possible is a direct way to reduce the risk of depression. In addition, the present study also highlights that more attention should be paid to the effects of environmental pollutions on mental illness, in addition to physical diseases.

As one kind of low molecular weight PAHs, naphthalene is mainly generated during a low or moderate temperature combustion process such as smoking (Cao et al. 2020a). Naphthalene is metabolized and excreted in urine as 1-OHNa and 2-OHNa. In the current study, we observed that the levels of urinary PAH metabolites were dramatically higher in smokers than in non-smokers, especially for 1-OHNa and 2-OHNa, and the associations between urinary PAH metabolites and depression were stronger among smokers than those among non-smokers. Interestingly, our previous study also noted that the association of inflammation with 1-OHNa and 2-OHNa was stronger in smokers than in non-smokers among Chinese urban adults (Zhou et al. 2018). Moreover, Zhou et al. (2016) have shown that PAH exposure has a stronger effect on lung function of smokers than non-smokers and that smoking may strengthen the adverse health effects of PAH exposure, which is similar to the findings in this study. These results have an important implication for public health that smoking cessation may be an effective approach to reducing PAH exposure and related adverse effects on health.

Although the potential mechanism between PAH exposure and depression remains largely unspecified, several tenable reasons may explain the associations. There is good evidence from in vitro and in vivo studies that neuroinflammation may participate in the pathophysiology of depression associated with PAHs (Felger and Lotrich 2013, Liu et al. 2012; Manzano-León et al. 2016). Meanwhile, recent animal and epidemiological studies revealed that PAHs could induce increased oxidative stress and cortisol release (Cao et al. 2020b; Cartolano et al. 2021). Hyperactivity of the

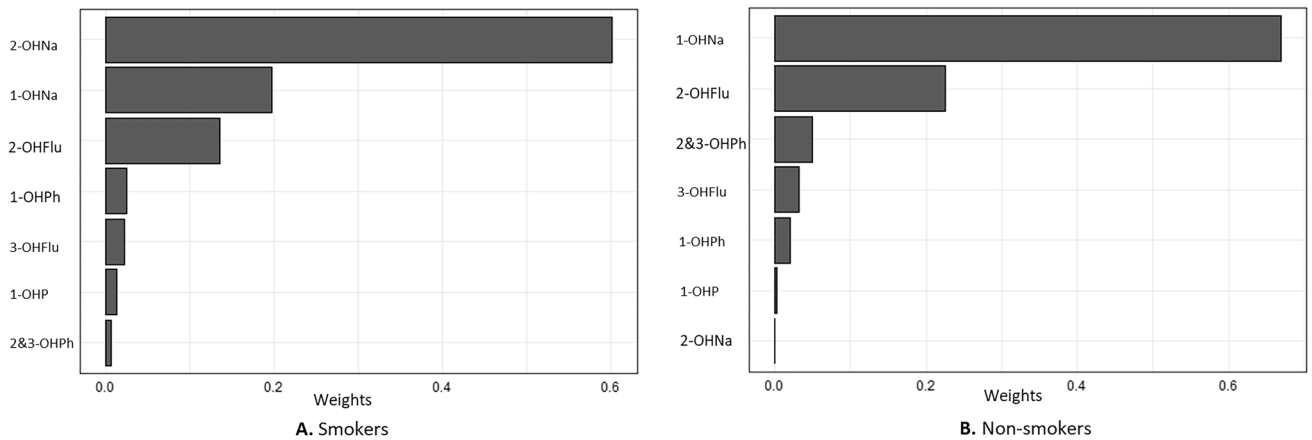

Fig. 1 Weights in the WQS regression between the risk of depression and WQS index of PAH mixtures (**A** smokers; and **B**. non-smokers). Adjusted for gender, age, BMI, race, education level, marital status, PIR, drinking status, physical activity, general health condition, and health insurance coverage. Abbreviation: 1-OHNa: 1-hydroxynaphthalene; 2-OHNa: 2-hydroxynaphthalene; 2-OHFlu: 2-hydroxyfluorene; 3-OHFlu: 3-hydroxyfluorene; 1-OHPh: 1-hydroxyphenanthrene; 2&3-OHPh: 2-hydroxyphenanthrene and 3-hydroxyphenanthrene; 1-OHP: 1-hydroxypyrene

hypothalamic–pituitary–adrenal axis, which regulates the stress responses and cortisol level, is implicated as a potential etiological factor for depression (Lopez-Duran et al. 2009; Penninx et al. 2013). Thus, PAHs may contribute to dysregulations of hypothalamic–pituitary–adrenal axis activity which increases the risk of depression (Cartolano et al. 2021; Lopez-Duran et al. 2009). Furthermore, PAH exposure was demonstrated to decrease leukocyte mitochondrial DNA content (Wong et al. 2017), which was also implicated in depression (Kim et al. 2011). To some extent, oxidative stress and mitochondrial DNA damage might also as potential mediating pathways for PAH-associated depression. In addition, PAHs also showed a negative impact on the development of the central dopaminergic system and structural brain changes (Cho et al. 2020; Yokota et al. 2009). Kleinridders et al. (2015) and Berkins et al. (2021) found that the alterations of dopamine and brain volumes might promote the development of depression. Of course, more researches are warranted to focus on the underlying mechanisms.

Several strengths should be acknowledged in this study. This study demonstrated positive associations between urinary PAH metabolites and depression risk based on a large and well-designed representative sample in the US, which could extend to the broader population. In addition to multiple logistic regression models, we also applied the WQS regression which also confirmed the association between mixed PAH exposure and depression. Of course, several limitations also existed in this study. First, this study could not draw a causal relationship due to the cross-sectional design, and only provides a new clue to support and establish hypotheses for further studies. Second, although urinary PAH metabolite concentrations are widely used to represent exposure to PAHs in humans, it was unlikely to use single spot urinary PAH metabolites to accurately estimate long-term PAH exposure. Thus, monitoring long-term PAH exposure by collecting multiple-point urine samples will be for more reliable conclusions in future researches. Third, the PHQ-9 is not a golden standard for diagnosing clinical depression. However, the PHQ-9 has been proved to be a valid tool with high specificity and sensitivity in evaluating symptoms of depression (Spitzer et al. 1999). Finally, even if multiple potential confounders were adjusted as well as possible, we could not cover all confounders that existed in this study.

Conclusion

Urinary PAH metabolites were positively associated with the risk of depression among US adults. Cigarette smoking not only significantly increased the levels of PAH exposure, but also partly strengthened the positive associations between PAH exposure and depression. Reducing exposure to PAHs, including smoking cessation, may be an effective way to reduce the risk of depression.

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Author contribution X. F. and W. C. designed the research. X. F. conducted the research, analyzed the data, and wrote the paper. R. L., D. S., D. W., Y. G., W. Q., M. C., T. X., C. D., M. Z., and W. C. contributed to the acquisition, analysis, or interpretation of the data, and revised the manuscript for important intellectual content. W. C. has primary responsibility for final content and is the study guarantor. All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data anaterials No additional data available.

Declarations

Ethics approval and consent to participate The National Health and Nutrition Examination Survey protocol was approved by the National Center for Health Statistics Ethics Review Board and written informed consent was obtained from all participants.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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