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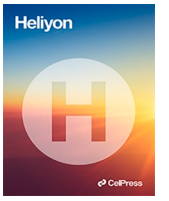

Association of chronic cough with exposure to polycyclic aromatic hydrocarbons in the US population

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are environmental pollutants formed during the incomplete combustion of organic substances, such as coal and oil. PAHs exposure is known to increase the incidence of respiratory diseases; however, limited research has focused on their impact on chronic cough. In this study, we utilized data from the National Health and Nutritional Examination Surveys (NHANES) from 2003 to 2012. Chronic cough was defined as 'coughing most days for three consecutive months or more'. Employing survey-weighted multivariate logistic regression models, we identified positive associations between all six PAHs metabolites (1-NAP, 2-NAP, 3-FLU, 2-FLU, 1-PHE, and 1-PYR) found in urine and the presence of chronic cough. Furthermore, results from restricted cubic spline modeling revealed a nonlinear relationship between urinary levels of 1-NAP, 2-NAP, 3-FLU, 2-FLU, and 1-PYR and the risk of chronic cough. Co-exposure modeling unveiled the combined effects of multiple exposures and the relative contributions of each PAHs. Notably, co-exposure to PAHs was positively associated with an increased risk of chronic cough, where 2-FLU emerged as the primary contributor to this association. These findings were particularly pronounced in individuals with high cotinine exposure ($\geq$0.05 ng/mL). In conclusion, this study presents epidemiological evidence linking PAHs exposure to an elevated risk of chronic cough. Further prospective investigations are warranted to corroborate these findings.

1. Introduction

Coughing serves as both a voluntary behavior and an uncontrollable reflex, functioning as a physiological defense mechanism to clear respiratory secretions and foreign bodies [1,2]. However, in some individuals, coughing can manifest as a persistent, excessive, and debilitating condition [3]. Chronic cough in adults is defined as a cough that lasts for more than 8 weeks [4]. Studies show that approximately 5%–10 % of adults suffer from chronic cough, and in the United States, the prevalence surpasses 10 % [5]. This condition leads to various complications, including upper respiratory, chest, cardiac, central nervous system, and psychological damage [1]. Notably, many patients experience symptoms of anxiety and insomnia, which significantly compromise their quality of life [6]. Furthermore, chronic cough places a substantial financial burden on both patients and the healthcare system [7].

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Traditionally, conditions such as asthma, chronic bronchitis, and laryngeal dysfunction have been associated with chronic cough in adults [8]. However, it is essential to recognize that not all patients with these conditions develop chronic cough. In addition, certain medications, like angiotensin-converting enzyme inhibitors, can exacerbate cough sensitivity [9]. Recently, environmental factors have garnered considerable attention in the etiology of chronic cough [10]. Consequently, it is of utmost public health importance to identify risk factors for chronic cough and develop appropriate preventive strategies.

Polycyclic aromatic hydrocarbons (PAHs) are pervasive environmental pollutants primarily generated from the incomplete combustion and pyrolysis of organic substances, including tobacco, petroleum products, and fossil fuels [11]. PAHs are volatile and constitute a significant component of air pollutants; they can traverse long distances through the atmosphere before settling in soil, vegetation, or water through atmospheric precipitation [12]. Inhalation, ingestion of contaminated food, and dermal contact are the primary routes of PAHs exposure [13]. PAHs undergo metabolism through mixed-function oxidative enzymes located in the endoplasmic reticulum of cells. This process leads to the excretion of resulting metabolites, primarily in the urine. Among these metabolites, monohydroxy PAHs, such as naphthalene, phenanthrene, fluorene, and pyrene, are commonly utilized as biomarkers to assess PAHs exposure [14]. Notably, exposure to PAHs has been associated with various adverse health effects, including inflammation, oxidative stress, cancer, and cardiovascular disease [13]. Recent studies have demonstrated that exposure to PAHs increases the risk of asthma and chronic bronchitis [15,16]. However, the specific etiology of chronic cough varies among patient populations, indicating the presence of unique cough endotypes [17].

The precise influence of environmental factors on chronic cough remains ambiguous. For instance, despite higher annual levels of ambient particulate matter in Asia compared to Europe and the United States, the incidence of chronic cough is lower in Asia [18]. Conversely, studies within various populations have revealed a link between exposure to ambient particulate matter and chronic cough, suggesting an environmental dimension in chronic cough development [19]. However, epidemiologic investigations into the association between PAHs exposure and chronic cough are still limited. In a small-sample longitudinal study by Anyenda E.O. et al., based on 88 patients with chronic cough, it was demonstrated that PAHs exposure was linked to an increased incidence of cough, particularly in the non-asthmatic group [20]. Furthermore, a US pediatric asthma cohort study involving 315 individuals revealed that exposure to environmental PAHs increased the incidence of asthma (1.01 (95 % CI, 1.00–1.02) to 1.10 (95 % CI, 1.04–1.17)) [21]. It's crucial to note that these studies had small sample sizes and some bias, as the populations studied were based on patients with chronic cough or asthma and did not include healthy individuals. In light of this, our present study explores the potential association between PAH exposure and chronic cough in a larger sample size. Additionally, we investigate potential synergistic or antagonistic effects among PAHs using a mixed-exposure model, examining the relationship between six PAHs metabolic mixtures and chronic cough. Our findings contribute valuable epidemiological evidence supporting the link between single and combined PAHs exposures and chronic cough, complementing existing research.

2. Material and methods

2.1. Study design and population

The National Health and Nutritional Examination Surveys (NHANES) is a population-based epidemiological survey program administered by the United States Centers for Disease Control and Prevention (CDC). For this study, we utilized data from five survey cycles conducted between 2003 and 2012, comprising participants aged 20 years or older who provided complete information on urinary PAHs, presence of chronic cough, and core covariates. The final dataset included 4301 US adults, among whom 465 reported having chronic cough. The chronic cough status was determined by healthcare professionals, and participants were asked, " Do you usually cough on most days for 3 consecutive months or more during the year?" The NHANES program received approval from the Ethics Review Board of CDC.

2.2. Exposure assessment

The NHANES Laboratory Protocols webpage provides a comprehensive description of the laboratory methods and procedures employed. In brief, urine samples were meticulously preserved at −20 °C, and the concentrations of six urinary PAHs metabolites were quantified employing the precise technique of isotope dilution high-performance gas/liquid chromatography-tandem mass spectrometry. These metabolites encompassed 1-hydroxynaphthalene (1-NAP), 2-NAP, 3-hydroxyfluorene (3-FLU), 2-FLU, 1-hydroxyphenanthrene (1-PHE), and 1-hydroxypyrene (1-PYR). In cases where the concentrations of PAHs fell below the limit of detection (LOD), a robust statistical estimation approach was applied, utilizing the formula LOD divided by the square root of 2. Furthermore, to account for variations in urine concentration, the PAHs concentrations were meticulously adjusted for urinary creatinine and subsequently expressed as ng/g creatinine.

2.3. Covariates

Covariates were selected based on prior epidemiological research that has examined associations between pollutant exposure and chronic cough [22]. Covariates included in this study were sex (male/female), age group (20–59 and $\geq$ 60 years), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), marital status (unmarried, separated, married), body mass index (BMI), educational attainment (lower than high school, high school or equivalent, above high school), household poverty-to-income ratio (PIR), alcohol (drinking at least 12 times per year), hypertension, and serum cotinine concentrations (markers

of environmental tobacco smoke (ETS) exposure with a cut-off point of 0.05 ng/mL) [23]. Additionally, we accounted for the primary risk factors for chronic cough, specifically chronic bronchitis and asthma [3].

2.4. Statistical analysis

We conducted a comprehensive baseline assessment of the various chronic cough states using chi-square, Mann-Whitney U, and t-tests for comparison. Urinary PAHs concentrations underwent a log transformation (Ln) to achieve a normal distribution and were categorized into quartiles (Q1-Q4) for categorical analysis. The Pearson correlation coefficient (r) measured the relationship between log-transformed PAHs concentrations. Accounting for NHANES' complex multistage sampling design, our analyses incorporated official NHANES sample weights, adjusted by dividing them by the number of periods included. Survey-weighted multiple logistic regression examined the association between PAHs and chronic cough. To investigate the dose-response relationship between PAHs and chronic cough, we employed restricted cubic spline (RCS) logistic regression models. All analyses adjusted for covariates, including sex, age, race, marital status, BMI, education, PIR, drinking, serum cotinine, hypertension, chronic bronchitis, and asthma. Subgroup analyses examined differences related to tobacco exposure.

To assess the cumulative impact of mixed PAHs exposure, this study employed weighted quantile sum (WQS) regression modeling [24]. A WQS index was constructed using quartiles of the urinary PAHs metabolic mixture. The resulting outcomes were interpreted in terms of the effect of a one-unit increase in the PAHs mixture on chronic cough, enabling the identification of significant chemicals

Table 1
Basic characteristics of participants by chronic cough in the U.S. adults, NHANES 2003–2012.

Characteristics	Participants			*P* value
	Total	Chronic cough	Non- Chronic cough	
Number	4301	465 (10.8)	3836(89.2)	
Gender				
male	2186 (50.8)	239(51.4)	1947 (50.8)	0.794
female	2115(49.2)	226 (48.6.)	1889(49.2)	
Age				
age (20–59)	2315 (53.8)	233 (50.1)	2082 (54.3)	0.089
age ≥60	1986 (46.2)	232 (49.9)	1754 (45.7)	
Race				
Mexican American	683 (15.9)	54 (11.6)	629 (16.4)	**<0.001**
Other Hispanic	282 (6.6)	20 (4.3)	262 (6.8)	
Non-Hispanic white	2225 (51.7)	312 (67.1)	1913 (49.9)	
Non-Hispanic black	870 (20.2)	61 (13.1)	809 (21.1)	
Other race	241 (5.6)	18 (3.9)	223 (5.8)	
Marital status				
Unmarried	614 (14.3)	75 (16.1)	539 (14.1)	**0.003**
Separated	1199 (27.9)	155 (33.3)	1044 (27.2)	
Married	2488 (57.8)	235 (50.5)	2253 (58.7)	
Education				
Lower than high school	1220 (28.4)	146 (31.4)	1074 (28.0)	**0.008**
High school or equivalent	1032 (24.0)	129 (27.7)	903 (23.5)	
Above high school	2049 (47.6)	190 (40.9)	1859 (48.5)	
Serum cotinine (ng/mL)	60.31 ± 134.81	129.38 ± 175.65	51.93 ± 126.47	**<0.001**
BMI	29.07 ± 6.50	29.41 ± 8.43	29.03 ± 6.22	0.241
PIR	2.69 ± 1.64	2.38 ± 1.62	2.72 ± 1.64	**<0.001**
Drinking				**0.011**
Drinker	1254 (29.2)	112 (24.1)	1142 (29.8)	
Non-drinker	3047 (70.8)	353 (75.9)	2694 (70.2)	
Hypertension				**<0.001**
Yes	1871 (43.5)	246 (52.9)	1625 (42.4)	
No	2430 (56.5)	219 (47.1)	2211 (57.6)	
Chronic bronchitis				**<0.001**
Yes	161 (3.7)	79 (17.0)	82 (2.1)	
No	4140 (96.3)	386 (83.0)	3754 (97.9)	
Asthma				**<0.001**
Yes	173 (4.0)	59 (12.7)	114 (3.0)	
No	4128 (96.0)	406 (87.3)	3722 (97.0)	
Urine PAHs (ng/g)				
1-NAP	0.218 (0.674)	0.593 (1.526)	0.203 (0.589)	0.214
2-NAP	0.342 (0.622)	0.641 (1.421)	0.328 (0.544)	**<0.001**
3-FLU	0.008 (0.018)	0.020 (0.089)	0.007 (0.014)	**<0.001**
2-FLU	0.022 (0.042)	0.047 (0.156)	0.021 (0.032)	**<0.001**
1-PHE	0.014 (0.014)	0.018 (0.019)	0.014 (0.013)	**0.001**
1-PYR	0.009 (0.012)	0.013 (0.025)	0.008 (0.010)	**<0.001**

Normally distributed continuous variables were expressed as mean ± SD; non-normally distributed continuous variables are expressed as median (IQR); Categorical variables were presented as n (%). n, numbers of subjects; %, weighted percentage.

within the mixture. It is important to note that the WQS regression model constrains the direction of individual chemical effects to ensure uniform impact across all chemicals. To explore the joint effects while relaxing the restriction of directional homogeneity and to comprehensively investigate parametric inference, we utilized a quantile g-computation (qgcomp) model [25]. This approach allowed us to determine both positive and negative weights of each PAHs metabolite in the cumulative effect of PAHs mixture exposure on chronic cough. Recognizing the potential for nonlinear and nonadditive dose-response relationships associated with exposure to chemical mixtures and the presence of multicollinearity [26], we further applied Bayesian kernel machine regression (BKMR) modeling to validate our previous findings. In this analysis, we assessed the cumulative effect of PAHs exposure on chronic cough by incrementally adjusting every 5th percentile while maintaining all other PAHs at specific percentiles. Moreover, we elucidated the response function of individual PAHs exposure on chronic cough by fixing one PAHs metabolite at varying percentiles (10th, 50th, and 90th) while keeping other chemicals at their median values. Additionally, we calculated post-inclusion probabilities (PIPs) to identify the PAHs with the most substantial impact on chronic cough risk.

Several sensitivity analyses were conducted to enhance the study's reliability. Firstly, the association between PAHs (single or in co-exposure) and chronic cough was reassessed by excluding subjects with pre-existing chronic bronchitis and asthma. Secondly, differences in the association between PAHs co-exposure and chronic cough across age, sex, and BMI subgroups were assessed. Finally, to further evaluate the cumulative exposure risk of PAHs, beta coefficients (β) of PAH metabolites associated with chronic cough were calculated using an adaptive elasticity network (AENET). Based on these β values, individual Environmental Risk Scores (ERS) were computed, representing the weighted sum of PAHs co-exposures. This scoring system has proven to be a valid tool for assessing cumulative disease risk from exposure to chemical mixtures [27,28]. ERS was categorized into quartiles, and the association between increasing ERS quartiles and chronic cough was analyzed using multiple logistic regression.

Statistical analysis was performed using R (version 4.2.3), with the utilization of the "gWQS", "bkmr", "qgcomp", "glmnet" and "gcdnet" packages for the respective analyses. The significance level chosen for the study was $P < 0.05$.

3. Results

3.1. Population characteristics and PAHs distribution

A total of 50,912 participants were initially enrolled in this study. After excluding individuals under 20 years of age (23,179) and those with missing covariates and urinary PAHs concentrations, the final sample included 4301 participants, with 465 (10.8 %) diagnosed with chronic cough. Table 1 provides an overview of the participants' general characteristics. We observed no statistical differences in age, sex, or BMI between the subgroups with and without chronic cough. However, statistical differences were found in race, marital status, education, serum cotinine, PIR, alcohol consumption, hypertension, chronic bronchitis, and asthma. Additionally, we observed statistically significant differences ($P < 0.01$) in the concentrations of 2-NAP, 3-FLU, 2-FLU, 1-PHE, and 1-PYR, which

Table 2
Association of PAHs with chronic cough, NHANES, 2003–2012.

PAHs	Continuous	Q1	Q2	Q3	Q4	*P* for trend
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	
1-NAP						
Overall	**1.19 (1.10,1.29)**	Reference	0.72 (0.46,1.12)	1.09 (0.73,1.62)	**2.07 (1.44,2.98)**	<0.001
Cotinine (low)	1.09 (0.95,1.26)	Reference	0.69 (0.38,1.26)	0.89 (0.50,1.59)	1.33 (0.70,2.51)	0.267
Cotinine (high)	**1.37 (1.23,1.52)**	Reference	0.77 (0.38,1.57)	1.44 (0.82,2.55)	**3.46 (2.09,5.73)**	<0.001
2-NAP						
Overall	**1.33 (1.15,1.54)**	Reference	0.91 (0.60, 1.38)	1.00 (0.67,1.49)	**2.01 (1.39,2.91)**	<0.001
Cotinine (low)	0.78 (0.58,1.06)	Reference	0.64 (0.37,1.11)	0.70 (0.40, 1.22)	0.78 (0.36,1.68)	0.388
Cotinine (high)	**1.91 (1.61,2.26)**	Reference	1.67 (0.86, 3.23)	1.72 (0.93,3.16)	**4.71 (2.76,8.04)**	<0.001
3-FLU						
Overall	**1.45 (1.27,1.64)**	Reference	0.69 (0.45,1.06)	0.97 (0.64,1.45)	**2.11 (1.42,3.13)**	<0.001
Cotinine (low)	1.04 (0.75,1.45)	Reference	0.74 (0.43,1.28)	1.05 (0.61,1.81)	0.98 (0.35,2.76)	0.628
Cotinine (high)	**1.69 (1.47,1.94)**	Reference	0.63 (0.30,1.31)	0.89 (0.46,1.73)	**2.86 (1.63,5.01)**	<0.001
2-FLU						
Overall	**1.49 (1.30,1.72)**	Reference	0.89 (0.58,1.37)	0.86 (0.56,1.30)	**2.44 (1.65,3.62)**	<0.001
Cotinine (low)	1.07 (0.74,1.55)	Reference	1.06 (0.62,1.80)	1.16 (0.66,2.05)	1.38 (0.54,3.53)	0.899
Cotinine (high)	**1.79 (1.52,2.11)**	Reference	0.61 (0.29,1.28)	0.53 (0.28,1.01)	**2.61 (1.54,4.41)**	<0.001
1-PHE						
Overall	**1.25 (1.06,1.48)**	Reference	1.11 (0.73,1.71)	1.21 (0.81,1.80)	**1.55 (1.06,2.27)**	0.105
Cotinine (low)	1.03 (0.76,1.41)	Reference	0.90 (0.50,1.62)	0.89 (0.49,1.61)	0.95 (0.50,1.81)	0.979
Cotinine (high)	**1.61 (1.32,1.98)**	Reference	1.60 (0.87,2.93)	**1.87 (1.07,3.29)**	**3.10 (1.86,5.18)**	<0.001
1-PYR						
Overall	**1.26 (1.10,1.46)**	Reference	0.98 (0.66,1.47)	0.83 (0.55,1.25)	**1.56 (1.06,2.29)**	0.007
Cotinine (low)	1.00 (0.74,1.36)	Reference	1.12 (0.67,1.87)	0.60 (0.32,1.15)	0.85 (0.38,1.90)	0.263
Cotinine (high)	**1.58 (1.34,1.86)**	Reference	0.75 (0.39, 1.44)	1.08 (0.60,1.93)	**2.36 (1.41,3.95)**	<0.001

Models were adjusted for gender, age, race, education, marital status, serum cotinine, BMI, PIR, drinking, hypertension, chronic bronchitis, asthma. Continuous, ln-transformed concentration of variables; Q, quartile.
Bold: $P < 0.05$.

were higher in the chronic cough population.

Table S1 presents the detection rates and concentration distributions of PAHs in urine, with all PAHs detected at rates exceeding 90 %. The highest urinary PAHs concentration was observed for 2-NAP, followed by 1-NAP and 2-FLU. Fig. S1 illustrates the correlation coefficients between Ln-transformed PAHs. This study revealed a high correlation (r = 0.96) between the concentrations of 2-FLU and 3-FLU in the urine samples. Furthermore, other PAHs also exhibited varying degrees of correlation, with coefficients ranging from 0.36 to 0.73.

3.2. Single PAHs exposures and chronic cough

Table 2 presents the results of the weighted logistic regression models. The findings indicate a significantly elevated risk of chronic cough in the highest quartile (Q4) of all PAHs exposures when compared to the lowest quartile (Q1) (1-NAP: 2.07 (1.44, 2.98); 2-NAP: 2.01 (1.39, 2.91); 3-FLU: 2.11 (1.42, 3.13); 2-FLU: 2.44 (1.65, 3.62); 1-PHE: 1.55 (1.06, 2.27); 1-PYR: 1.56 (1.06, 2.29)).

Stratified analyses were conducted based on serum cotinine exposure levels, indicating that the risk of chronic cough from PAHs exposure was more pronounced in the high cotinine exposure (≥0.05 ng/mL) population. In this subgroup, the highest quartile Q4 exposures (compared to quartile Q1) exhibited increased risk of chronic cough for 1-NAP: 3.46 (2.09, 5.73), 2-NAP: 4.71 (2.76, 8.04), 3-FLU: 2.86 (1.63, 5.01), 2-FLU: 2.61 (1.54, 4.41), 1-PHE: 3.10 (1.86, 5.18), and 1-PYR: 2.36 (1.41, 3.95). Additionally, the risk of chronic cough exhibited a dose-dependent relationship with increasing concentrations of all PAHs in urine ($P < 0.05$ for trend). Conversely, no association was found between any single PAHs exposure and chronic cough in the cotinine low-exposure (<0.05 ng/mL) population ($P > 0.05$).

Furthermore, this study employed RCS to evaluate non-linear associations between urinary PAHs levels and chronic cough. The results revealed non-linear associations between PAHs metabolites, specifically 1-NAP, 2-NAP, 3-FLU, 2-FLU, and 1-PYR, and the risk of chronic cough (all P nonlinear <0.05) (Fig. S2). Although the linear trend test revealed specific linear relationships within quartiles (trend $P < 0.05$), the RCS analysis proved more adept at capturing intricate nonlinear associations spanning the entire range.

3.3. PAHs co-exposure and chronic cough

WQS modeling results revealed a significant increase in the risk of chronic cough (1.33, 1.13–1.58) due to co-exposure to PAHs (refer to Fig. 1A). Of note, the primary weights assigned to individual PAHs were as follows: 2-FLU (0.488), 3-FLU (0.178), 1-PHE (0.127), 1-NAP (0.116), and 2-NAP (0.079) (refer to Fig. S3 and Table S2 for details). Subgroup analyses, stratified by cotinine levels, demonstrated a stronger positive correlation between concurrent PAHs exposure and chronic cough in the high cotinine-exposed population (2.13, 1.76–2.58). However, this correlation did not reach statistical significance in the low cotinine-exposed population. In the cotinine high-exposure population, 1-NAP, 2-NAP, and 3-FLU (weights of 0.348, 0.310, and 0.224, respectively) were the highest-weighted PAHs.

The qgcomp model estimated exposure weights encompassing both positive and negative values. These results were in alignment with the WQS model, demonstrating significant associations between cumulative PAHs exposure and the risk of chronic cough in both the overall population (1.03, 1.02–1.04) and the high cotinine-exposure subpopulation (1.08, 1.06–1.09) (see Fig. 1B). With the exception of 1-PYR, all PAHs exhibited substantial positive influences on the overall relationship with chronic cough. For a detailed breakdown of the positive and negative weights associated with each PAHs, please refer to Fig. S4.

Fig. 2 (A-C) presents the overarching relationship between PAHs mixtures and the heightened susceptibility to chronic cough. Evidently, a significant upsurge in chronic cough risk is discernible within the range of PAHs mixture levels extending up to the 70th percentile. Conversely, in the population exposed to cotinine, significant effects are evident at exposure levels exceeding the 50th percentile. Estimated PIPs for 2-FLU (PIP = 0.98), 2-NAP (PIP = 0.87), 1-PHE (PIP = 0.73), and 3-FLU (PIP = 0.52), exceeding the 0.5

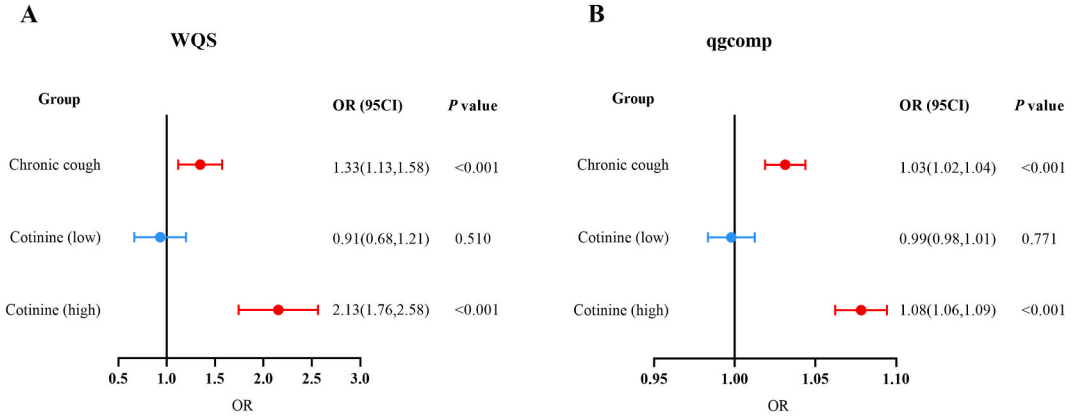

Fig. 1. Common effects of PAHs mixtures on chronic cough estimated by WQS and qgcomp models. (A) WQS model results. (B) qgcomp model results.

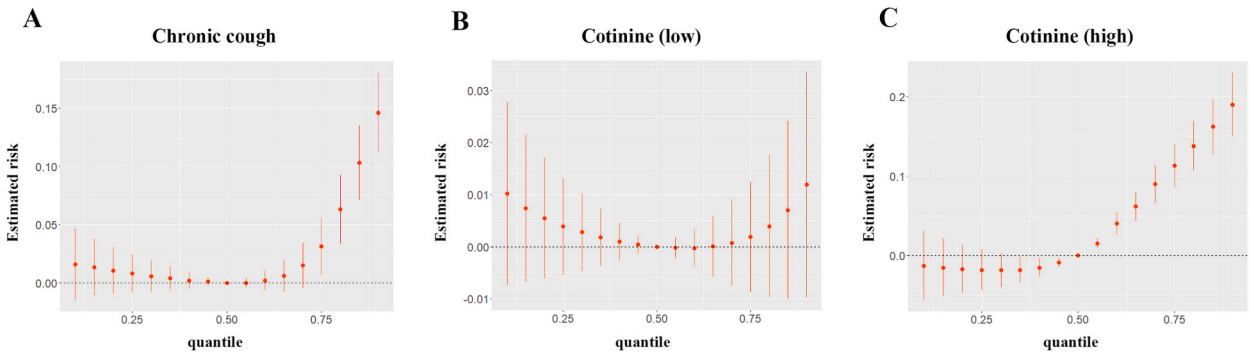

Fig. 2. Common effects of PAHs mixtures on chronic cough estimated by BKMR modeling. (A) Total. (B) Cotinine (low). (C) Cotinine (high).

threshold, suggest that these PAHs are significant predictors associated with chronic cough risk (Table S3). Furthermore, within the cotinine high-exposure population, a notable effect of 2-FLU exposure on chronic cough risk was observed when 2-FLU values were fixed at the 50th or 90th percentile, while the remaining PAHs were set at the median (Fig. 3C). Contrarily, no statistically significant effects were discerned within the general and low cotinine-exposed populations (Fig. 3A and B).

3.4. Sensitivity analysis

The results are summarized as follows: firstly, after excluding participants with chronic bronchitis or asthma (n = 286), the impact of PAHs, either as single or mixed exposures, on the risk of chronic cough increased compared to the pre-exclusion phase. Specifically, the risk ratios were as follows: 1-NAP: 1.19 (1.10, 1.30), 2-NAP: 1.36 (1.17, 1.59), 3-FLU: 1.49 (1.29, 1.71), 2-FLU: 1.51 (1.29, 1.76), 1-PHE: 1.25 (1.04, 1.51), 1-PYR: 1.31 (1.12, 1.52), Mixture of WQS: 1.62 (1.32, 2.00), Mixture of qgcomp: 1.03 (1.01, 1.04) (see Table 3). Secondly, the assessment of age, gender, and BMI effects on the PAHs-chronic cough relationship revealed no substantial moderating effects in subgroup analysis (refer to Table S4). Thirdly, including ERS by quartiles in multivariate logistic regression showed that an increase in ERS quartiles significantly correlated with an elevated risk of chronic cough: 1.000 (reference), 0.815 (0.573, 1.157), 1.178 (0.850, 1.636), and 2.599 (1.869, 3.635), respectively. The linear trend test indicated a significant linear trend between ERS and the risk of chronic cough (trend $P < 0.001$) (refer to Tables S5 and S6).

4. Discussion

To the best of our knowledge, this study represents the first comprehensive investigation into the potential association between PAHs exposure, whether single or combined, and the risk of chronic cough among adults in the United States in a nationally representative and relatively large sample size. Our results indicate a significant elevation in chronic cough risk with exposure to any of the PAHs. Moreover, mixed exposure modeling consistently reveals a substantial positive association between concurrent exposure to elevated PAHs levels and the risk of chronic cough. This association is notably pronounced in the high cotinine-exposure subgroup.

In adults, chronic cough frequently results from hypersensitivity reactions, often triggered by exposure to low levels of heat or chemicals [29]. Such exposure can lead to the dysregulation of neural pathways and receptors within the central nervous system and ganglia, subsequently giving rise to persistent cough [30]. Additionally, multiple personal and environmental factors, including respiratory infections, occupational irritants, allergens and environmental pollution, have the potential to sensitize and initiate cough,

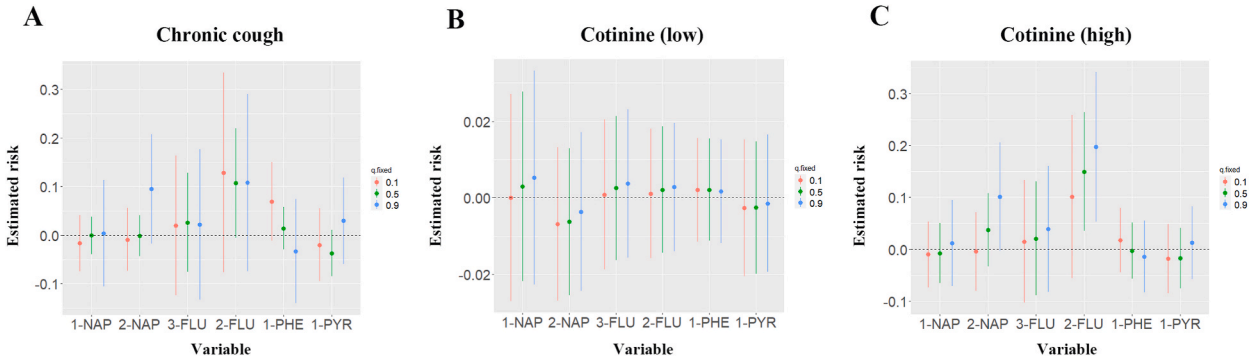

Fig. 3. The BKMR model estimated the correlation between a single PAHs and the risk of chronic cough while keeping all other PAHs at the corresponding percentile levels. (A) Total. (B) Cotinine (low). (C) Cotinine (high).

Table 3
Associations of chronic cough with PAHs: survey-weighted logistic regression analysis for continuous variables and mixture of WQS and qgcomp analysis, excluding chronic bronchitis, and asthma populations.

Variables	Continuous	Q1	Q2	Q3	Q4	*P* trend
	OR (95%CI)		OR (95%CI)	OR (95%CI)	OR (95%CI)	
1-NAP	**1.19 (1.10,1.30)**	ref	0.68 (0.41,1.12)	1.08 (0.71,1.66)	**1.94 (1.30,2.89)**	<0.001
2-NAP	**1.36 (1.17,1.59)**	ref	0.97 (0.62,1.52)	0.94 (0.59,1.47)	**1.98 (1.32,2.98)**	<0.001
3-FLU	**1.49 (1.29,1.71)**	ref	0.74 (0.46,1.20)	1.01 (0.64,1.59)	**2.25 (1.45,3.50)**	<0.001
2-FLU	**1.51 (1.29,1.76)**	ref	0.85 (0.52,1.37)	0.79 (0.50,1.26)	**2.49 (1.62,3.84)**	<0.001
1-PHE	**1.25 (1.04,1.51)**	ref	1.19 (0.73,1.94)	1.28 (0.82,2.00)	**1.63 (1.06,2.51)**	0.130
1-PYR	**1.31 (1.12,1.52)**	ref	0.94 (0.59,1.47)	0.91 (0.58,1.42)	**1.63 (1.07,2.47)**	0.009
Mixture of WQS	**1.62 (1.32, 2.00)**	–	–	–	–	<0.001
Mixture of qgcomp	**1.03 (1.01, 1.04)**	–	–	–	–	<0.001

Models were adjusted for gender, age, race, education, marital status, serum cotinine, BMI, PIR, drinking, hypertension. Continuous, ln-transformed concentration of variables.
Bold: $P < 0.05$.

rendering them potential risk factors for chronic cough [31]. Currently, there is insufficient evidence regarding the relationship between environmental pollutant exposure and the risk of chronic cough. A greater proportion of research has been dedicated to investigating the connections between environmental pollutant exposure and conditions such as asthma, bronchitis, and chronic obstructive pulmonary disease (COPD). Remarkably, a population-based study conducted in China revealed a significantly higher prevalence of chronic cough in urban households compared to rural households. This disparity was attributed primarily to indoor exposure to particulate matter (PM10) [32]. Furthermore, a separate investigation, centering on the ramifications of prolonged exposure to traffic-related air pollution, unveiled a heightened prevalence of chronic cough among individuals residing in close proximity to major traffic arteries [33]. It is worth noting that PAHs constitute a noteworthy constituent of particulate matter and vehicular exhaust pollution. Nevertheless, research endeavors specifically scrutinizing the precise correlations between PAHs exposure and chronic cough remain somewhat scarce.

The association between PAHs and chronic cough reported in this study is mechanistically plausible. PAHs share common exposure pathways with other environmental pollutants, eliciting similar effects on respiratory symptoms through mechanisms involving oxidative stress and dysregulation of the aryl hydrocarbon receptor (AhR) signaling pathway [34,35]. Numerous studies have demonstrated a significant dose-effect relationship between PAHs exposure and oxidative stress marker levels [36,37]. This, in turn, induces airway eosinophilic inflammation and exacerbates atopic sensitization, which is a primary cause of cough [38]. Moreover, noxious irritants, inflammation, and oxidative stress contribute to an increase in intracellular calcium, activating P2X3 channels on sensory nerves. This leads to cellular depolarization and triggers action potentials transmitted via the vagus nerve to the central nervous system, ultimately inducing cough [39]. Interestingly, exposure to environmental PAHs has been shown to trigger a rise in intracellular calcium ion concentration independently of AhR [40]. Furthermore, PAHs are implicated in calcium signaling within bronchial epithelial cells [41]. Considering these findings, there appears to be a plausible association between PAHs exposure and chronic cough.

This study revealed a clear dose-response correlation between individual exposure to 1-NAP, 2-NAP, 3-FLU, 2-FLU, and 1-PYR and the likelihood of chronic cough. Moreover, the findings from three complementary models consistently demonstrated a positive association between co-exposure to elevated levels of PAHs and the risk of chronic cough. These results align with a small longitudinal study involving 83 individuals, which indicated that environmental PAHs exposure, even at low levels, was linked to cough prevalence in adults with chronic cough [42]. Additionally, a European birth cohort study reported that exposure to PAHs in the second trimester significantly increased the risk of various respiratory symptoms in newborns, including wheezing, coughing, and sore throat, while also influencing the duration of respiratory symptoms [43]. Subgroup analyses revealed a more substantial effect of PAHs exposure on chronic cough in individuals with high cotinine exposure ($\geq$0.05 ng/mL), either single or in combination. Conversely, no discernible effect of PAHs on chronic cough was observed in the cotinine low-exposure (<0.05 ng/mL) population. Several explanations account for this observation. Firstly, serum cotinine levels serve as a crucial indicator of exposure to ETS, a significant source of PAHs exposure. Typically, tobacco users exhibit higher urinary biomarker concentrations of PAHs compared to non-tobacco users [44]. Similarly, in our study, elevated concentrations of all six urinary PAHs were observed in high cotinine-exposed populations compared to those with low cotinine exposure (data not shown). Additionally, extensive evidence has demonstrated that exposure to ETS significantly increases the risk of respiratory symptoms and serves as a prominent risk factor for chronic cough [45,46]. Based on these findings, we hypothesize that PAHs exposure may significantly contribute to the development of chronic cough induced by ETS exposure.

It is essential to highlight that in the mixed exposure analysis of qgcomp, we observed a negative effect of 1-PYR in both the overall population and the cotinine high-exposure subgroup. Several explanations underpin this observation. Firstly, as evident in the distribution of PAHs metabolite concentrations (Table S1), the concentration of 1-PYR is notably lower compared to the other PAHs, both in mean and geometric mean values. Moreover, a significant effect on chronic cough was observed in both 1-PYR single exposure models. In the BKMR model, 1-PYR concentrations displayed a positive trend at the 90th percentile. Furthermore, the AENET analysis yielded β of 0 for 1-PYR, indicating a minimal impact on chronic cough. Consequently, the observed negative effect of 1-PYR in the mixed exposure analysis can be considered negligible.

This study possesses several notable strengths. Firstly, it investigates the link between PAHs exposure and chronic cough using a

substantial dataset with comprehensive covariate information, addressing limitations present in previous studies. Secondly, the application of innovative statistical methods allows for a thorough evaluation of the effects of mixed PAHs exposure on chronic cough, ensuring the reliability of our results. Lastly, our research revealed an ETS-related connection between PAHs exposure and chronic cough risk, thereby contributing to potential disease prevention strategies.

Nevertheless, several limitations warrant consideration. Firstly, the data originated from the NHANES baseline survey, which precludes making causal inferences. Secondly, despite meticulous control for numerous confounders and the exclusion of patients with asthma and chronic bronchitis in sensitivity analyses, certain pivotal risk factors for chronic cough disease, such as gastroesophageal reflux disease and COPD, were unavailable due to constraints in NHANES data. Furthermore, the lack of detailed information on prescription drug use for hypertension prevented the inclusion of angiotensin-converting enzyme inhibitors in our analysis, potentially resulting in an overestimation of the impact of PAHs exposure. Lastly, it is imperative to clarify that tobacco represents only one major source of PAHs. Subsequent investigations should delve into the association between other sources of PAHs and the risk of chronic cough.

5. Conclusions

In conclusion, this cross-sectional study demonstrates a significant association between exposure to PAHs and an elevated risk of chronic cough. Moreover, co-exposure to a mixture of PAHs showed a substantial positive combined effect on chronic cough, with 2-FLU identified as the primary causative factor. Notably, these effects were more pronounced in the population highly exposed to cotinine. Nevertheless, to establish the reliability and causality of these findings, further prospective studies are warranted.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Miaomiao Jiang: Writing - review & editing, Writing - original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hui Zhao:** Writing - review & editing, Writing - original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23413.

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