



Association of polycyclic aromatic hydrocarbons and asthma among children 6–19 years: NHANES 2001–2008 and NHANES 2011–2012



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ABSTRACT

Background: Polycyclic aromatic hydrocarbons (PAHs) are a group of chemicals that can induce oxidative stress and related cytotoxicity. Whether environmental exposure of PAHs has effects on asthma in the general population is still unclear. This study investigated the association of urinary PAHs with asthma in U.S. children.

Methods: 15 447 children who participated in the US National Health and Nutrition Examination Survey 2001–2008 and 2011–2012 were studied. Ten urinary PAHs were analyzed for their association with asthma or asthma related symptoms. Multivariate logistic regression was applied to assess associations between urinary PAHs and asthma adjusted for age, gender, ethnicity, body mass index and the poverty income ratio.

Results: When stratified by age and sex, we found a remarkable association between urinary 2-phenanthrene and diagnosed asthma in boys (OR: 2.353, 95% CI: 1.156–4.792; $P = 0.021$) aged 13–19 years old. Positive association was observed between ever wheeze and 4-phenanthrene among girls aged 13–19 years (OR: 4.086, 95% CI: 1.326–12.584, $P = 0.043$). Moreover, an overall positive association between 1-pyrene and diagnosed asthma was observed. However, no association existed between levels of 1-naphthol, 2-naphthol, 3-fluorene, 2-fluorene, 3-phenanthrene, 1-phenanthrene or 9-fluorene with asthma or asthma symptom in this population.

Conclusions: This data provide epidemiological evidences that urinary PAHs are positively associated with asthma in children aged 6–19 years. However, the underlying mechanisms still need further exploration.

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1. Introduction

Asthma is one of the most common chronic diseases characterized by recurrent airway obstruction, bronchial hyper-responsiveness and airway inflammation. It is prevalent in developed countries, and is becoming increasingly common in developing countries due to the increased urbanization of communities. Asthma is also the most common chronic health condition among

children in the United States. Approximately 9 million children and 7 million adults are affected by this disease in the US (National Institutes of Health, 2009). One in 11 children and one in 12 adults have asthma, and this disease resulted in 10.5 million missed school days in children and 14.2 million lost working days in adults in 2008. The USA spends \$56 billion on asthma medications annually [1]. The prevalence of childhood asthma increased from 3.6% to 9.6% during 1980–2009 in the United States [2], especially in urban areas like New York city [3]. Some reports found that asthma is more prevalent in boys [4]. The potential determinants responsible for development of asthma include tobacco smoke exposure, obesity and lack of physical exercise, severe lower respiratory tract infections (such as pneumonia), dietary habits, and male gender, a small family size and a family history of asthma [5].

Polycyclic aromatic hydrocarbons (PAHs) are a group of chemicals formed during the incomplete combustion of coal, oil and gas,

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garbage and other organic substances. In general, people are exposed to mixtures of PAHs that originate from a wide range of sources as vehicle exhausts, asphalt, wild fires, coal tar, charbroiled foods, agricultural burning and tobacco smoke. Due to their lipophilic nature, PAHs enter the body quickly and easily absorbed by all routes of exposure and are readily and predominantly metabolized to hydroxylated metabolites and glucuronide metabolites. Blood and urine PAH levels have been proposed as specific biomarkers of PAH exposure via inhalation of polluted air and intake of certain foods (e.g. charcoal broiled meats and other smoked foods) [6].

PAHs have received particular attention due to their potential to induce oxidative stress and related cytotoxicity [7]. Several PAHs, including benz[a]anthracene, benzo[a]pyrene, and chrysene, have been classified as potential human and animal carcinogens. Because of the known health hazards associated with some of these compounds, human exposure to PAHs has long been a concern. There are studies reported that PAHs exposure has been associated with several adverse outcomes in children, including asthma symptoms, biomarkers of asthma, respiratory health, and cognitive development [8–11]. PAHs have also been linked to deficiency of pulmonary function and wheezing in children [12]. Some epidemic data also provide evidences that PAHs exposure in the child contribute to asthma morbidity [13,14]. However, little is known about the relationship between individual PAH exposure and pulmonary function in children.

The American National Health and Nutrition Examination Survey (NHANES) (2001–02, 2003–04, 2005–06, 2007–08, 2011–12) has recently provided comprehensive data of PAHs metabolites collected from a population of children and adults without suspected occupational exposures. PAHs levels detected in the children were higher, indicating that they may be at greater risk for various adverse health effects. In this study, we intended to use the cross-sectional data from NHANES to investigate the potential association between PAHs exposure and asthma in children. The data were extracted from the NHANES 2001–2008 and 2011–2012. In this analysis, we focused on PAHs among children aged 6–19 years, and the prevalence of self-reported wheezing or coughing and physician-diagnosed asthma. The study was restricted to children because asthma is primarily an early-onset disease, and thus measures of PAHs in children are more reflective of exposure prior to disease.

2. Materials and methods

2.1. Study population

The NHANES is a cross-sectional survey conducted by the US Centers for Disease Control and Prevention and designed to assess the health and nutritional status of adults and children in US since the early 1960's. Data are released every 2 years and the database is a publicly available resource for use by researchers throughout the world. About 5000 persons were recruited each survey year. All participants provided written informed consent, and the National Center for Health Statistics (NCHS) obtained institutional review board approval to conduct the surveys [15]. The NHANES data are representative of the non-institutionalized population of the U.S. because of the probability-based sampling methods used [15].

This analysis used data from the following five cycle: 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2011–2012. We did not utilize data from 2009 to 2010 cycle because this cycle did not contain data about PAHs. The present study sample consisted of NHANES participants aged 6–19 years who had a measured urine PAHs concentration and had data about the asthma related outcomes. The final study sample consisted of 15,447 children (7819

boys and 7628 girls).

2.2. Urinary polycyclic aromatic hydrocarbons measurement

PAHs metabolites were measured in spot urine samples from participants. Measurement of urinary metabolites indicates exposure to the parent PAHs. Urine specimens are processed, stored and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis. Urinary PAHs were analyzed by the following procedure: enzymatic hydrolysis of urine, solid-phase extraction, derivation, and analyzed by GC/HRMS (Laboratory procedure manual, see http://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/PAH_G.htm). Urinary creatinine, as a measurement of urinary dilution, was used to standardize the level of PAHs for urine dilution. The urinary creatinine was measured using Beckman Synchron CX3 Clinical Analyzer at the University of Minnesota. Of the 11 PAHs analyzed in NHANES, we excluded 3-fluoranthene since only one available data was analyzed during 2001–2002 cycle. Finally, the following 10 analytes were included in this study: 1-naphthol, 2-naphthol, 3-fluorene, 2-fluorene, 3-phenanthrene, 1-phenanthrene, 2-phenanthrene, 1-pyrene, 9-fluorene, 4-phenanthrene.

2.3. Asthma assessment

In order to assess asthma prevalence, children aged 6–19 years were asked whether a doctor or other health professional had ever diagnosed them with asthma (diagnosed asthma). Whether they usually cough on most days for 3 consecutive months or more during the year (ever cough). Whether they had wheezing or whistling in their chest in the past 12 months (ever wheeze). “Diagnosed asthma” was selected because of the long half-life of PAHs in the body, whereas “coughing most days” and “wheezing or whistling in the past year” were chosen to assess the sensitivity of recent respiratory symptoms to urine PAHs concentrations assessed cross-sectionally.

2.4. Covariants

Potential confounders thought to be association with PAHs and child asthma was controlled for the following: age, race, the poverty income ratio (PIR), body mass index (BMI) and gender. PIR was categorized as three level: low (<1), middle (1–2) and high (≥ 2). We used body mass index (BMI) to define obesity status. In children, overweight was calculated as BMI between the 85th and 95th percentiles, obesity was defined as a BMI greater than or equal to the 95th percentile and of the corresponding sex and age reference group [16]. Serum cotinine, a marker of exposure to environmental tobacco smoke, was excluded in the final analysis because it has a great effect on the outcome.

2.5. Statistical methods

The baseline characteristics of the sample are presented as mean values $\pm$ S.E. for the continuous ones and as proportions for categorical variables. We conducted independent t-tests to examine the differences of age and BMI between boys and girls among children aged 6–12 years and 13–19 years. Chi-square test was used to compare the difference of PIR, race, diagnosed asthma, ever cough and ever wheeze between boys and girls among children aged 6–12 years and 13–19 years. Otherwise, we used chi-square to examine the incidence of diagnosed asthma, ever cough and ever wheeze in each gender among children age 6–12 years and 13–19 years. Independent t-tests also conducted to examine the

differences of PAHs between those children who had asthma or asthma symptoms and those who did not have. The adjusted OR and 95% confidence intervals (CI) for association of asthma and PAHs exposure were estimated used weighted multiple variable logistic regression models. We also examined the adjusted level of 10 PAHs to find whether they were in a normal distribution. Each PAH was classified into quartiles, the first quartile was performed as the reference. We also used separate analyses stratified by sex and age (6–12, 13–19 years) as age and sex are important variables. ORs were adjusted for gender, age (years), race (Mexican-American, other Hispanic, non-Hispanic White, non-Hispanic Black, and Other Race-including multi-racial), PIR (tertiles) and BMI (tertiles). All analyses were conducted with the Statistical Analysis Systems software package version 9.2(SAS Institute, Inc., Cary, NC, USA). A two-tailed p-value <0.05 was considered as the cut-off for statistical significance.

3. Results

3.1. Study population characteristics

The sample population was composed of children aged 6–19 years who participated in NHANES between 2001 and 2008 and between 2011 and 2012. Table 1 presents the baseline characteristics of the participants (6–19 years) included in the present study. All data was stratified by sex and age. No difference was observed in the distribution of BMI or PIR between genders among children aged 6–12 years and 13–19 years. Occurrence of ever cough were the lowest both in boys and girls aged 6–19 years compared with the occurrence of diagnosed asthma and ever wheeze. The incidence of diagnosed asthma was the highest in boys aged 6–19 years compared with the incidence of other two asthma symptoms. While the incidence of ever wheeze was the highest in girls aged 6–19 years compared with the incidence of other two asthma symptoms.

3.2. Polycyclic aromatic hydrocarbons (PAHs)

Table 2 show the concentration of PAHs according to gender and the occurrence of asthma or asthma symptoms. The difference of concentration of PAHs was compared between subjects with and without asthma symptoms in each gender. Mean concentration of 1-phenanthrene and 1-pyrene was higher in boys who reported to

have asthma symptom. However, this difference was not found in girls. None of the ten PAHs showed difference between subjects with and without asthma symptoms in girls.

3.3. Polycyclic aromatic hydrocarbons and asthma symptom

In the multiple variable logistic regression of the association between urinary PAHs and asthma stratified by age and sex, we found that exposure to a higher concentration of PAH increased the risk for asthma or asthma symptom both in boys and girls after adjustment for age, gender, race, BMI and PIR (Table 3). The highest quartile of 2-phenanthrene showed a significantly increase of the risk of ever asthma compared with the lowest quartile among boys aged 13–19 years old (OR: 2.353, 95% CI: 1.156–4.792; $P = 0.021$). Similarly, positive association of ever wheeze with the highest concentrate of 4-phenanthrene was observed among girls aged 13–19 years (OR: 4.086, 95% CI: 1.326–12.584, $P = 0.043$). Table 4 present the association between PAHs exposure and asthma symptom not stratified by age and sex. We found that 1-pyrene had a 44.4% increase of the risk of diagnosed asthma (OR: 1.444, 95%CI: 1.003–2.080, $P = 0.039$).

4. Discussion

This is one of the first cross-sectional analyses to evaluate the association between urinary PAHs concentrations and asthma among U.S. children aged 6–19 years. We compared the incidence of three diseases in both gender and found that: the incidence of diagnosed asthma was highest in boys; ever wheeze was the highest in girls and the occurrence of ever cough was the lowest in both genders. After stratified by age and sex, the highest concentration of 2-phenanthrene showed a significantly increase for the risk of ever asthma among boys aged 13–19 years. Positive association was observed between ever wheeze and the highest quartile of 4-phenanthrene among girls aged 13–19 years. Overall, our results also indicated a positive association between urinary 1-pyrene and risk of diagnosed asthma.

Inhalation and dietary intake were the main sources of PAHs exposure in human. Ma et al. summarized that the daily intakes of PAHs via indoor air ingestion were 29,848 ng/day for adult and 11,342 ng/day for toddlers. In Asia, dietary exposure of PAHs was even higher, being 55,000 ng/day for adults and 31,350 ng/day for toddlers [17]. Yu et al. reported that the median concentrations of

Table 1
Population characteristics.

Variable	6–12 years		P	13–19 years		P
	Boy (n = 3596)	Girl (n = 3627)		Boy (n = 4223)	Girl (n = 4001)	
Mean ± SE						
Age(year)	9.07 ± 0.034	9.06 ± 0.034	0.008*	16.01 ± 0.030	15.87 ± 0.032	0.001*
BMI(kg/m ²)	25.18 ± 0.135	25.12 ± 0.133	0.06	25.31 ± 0.123	25.12 ± 0.124	0.26
Variable %						
Race			0.766			0.412
Mexican American	27.2%	27.8%		27.5%	28.6%	
Other Hispanic	7.2%	6.8%		5.8%	6.3%	
Non-HispanicWhite	27.4%	26.4%		27.3%	27.9%	
Non-Hispanic Black	30.5%	31.1%		33.0%	31.3%	
other	7.6%	8.0%		6.3%	6.0%	
PIR			0.262			0.064
<1	32.4%	33.5%		29.9%	32.4%	
1 to 2	27.6%	25.9%		27.0%	25.7%	
≥2	40.0%	40.5%		43.1%	42.0%	
diagnosed asthma	14.6%	13.4%	0.143	13.6%	13.9%	0.694
Ever cough	8.6%	8.0%	0.544	8.3%	8.8%	0.553
Ever wheeze	13.6%	13.6%	0.916	12.3%	14.5%	0.002*

PIR: poverty income ratio. *Statistically significant ($p < 0.05$).

Table 2Mean concentrate ($\pm$ SE) of certain PAHs among boys and girls, reporting diagnosed asthma, ever cough and ever wheeze.

Boys	No asthma symptoms(n = 3023)	Asthma symptoms(n = 1683)	p-value
1-naphthol	5.76 $\pm$ 2.729	3.50 $\pm$ 0.433	0.556
2-naphthol	5.79 $\pm$ 1.675	4.77 $\pm$ 0.596	0.669
3-fluorene	0.14 $\pm$ 0.009	0.19 $\pm$ 0.030	0.127
2-fluorene	0.31 $\pm$ 0.012	0.38 $\pm$ 0.052	0.174
3-phenanthrene	0.13 $\pm$ 0.006	0.16 $\pm$ 0.021	0.149
1-phenanthrene	0.13 $\pm$ 0.004	0.19 $\pm$ 0.028	0.039*
2-phenanthrene	0.06 $\pm$ 0.004	0.08 $\pm$ 0.011	0.148
1-pyrene	0.11 $\pm$ 0.008	0.16 $\pm$ 0.018	0.011*
9-fluorene	0.41 $\pm$ 0.084	0.48 $\pm$ 0.109	0.622
4-phenanthrene	0.03 $\pm$ 0.002	0.05 $\pm$ 0.014	0.224
Girls	No asthma symptoms(n = 2921)	Asthma symptoms(n = 1684)	p-value
1-naphthol	4.42 $\pm$ 0.990	3.14 $\pm$ 0.413	0.333
2-naphthol	4.45 $\pm$ 0.340	5.83 $\pm$ 0.745	0.092
3-fluorene	0.16 $\pm$ 0.013	0.18 $\pm$ 0.029	0.456
2-fluorene	0.37 $\pm$ 0.032	0.39 $\pm$ 0.048	0.637
3-phenanthrene	0.15 $\pm$ 0.018	0.16 $\pm$ 0.025	0.865
1-phenanthrene	0.19 $\pm$ 0.022	0.18 $\pm$ 0.014	0.736
2-phenanthrene	0.08 $\pm$ 0.009	0.08 $\pm$ 0.006	0.871
1-pyrene	0.13 $\pm$ 0.009	0.16 $\pm$ 0.017	0.066
9-fluorene	0.34 $\pm$ 0.026	0.38 $\pm$ 0.039	0.377
4-phenanthrene	0.04 $\pm$ 0.004	0.04 $\pm$ 0.006	0.911

*Statistically significant ($p < 0.05$).

total PAH₁₅ in human milk, placenta, and umbilical cord blood for the Beijing population reached 278, 819, and 1372 ng/g of fat, respectively [18]. These data indicated that children are the most vulnerable group in society exposed to PAHs in the daily life. Therefore, an association between urinary PAHs concentrations and asthma among U.S. children in this study using data from NHANES study could be expected.

Exposure to PAHs has been linked to several adverse outcomes in children, including respiratory health [10]. Our finding that exposure to PAHs enhanced the risk of asthma is consistent with previous reports [8,19–22]. One study found that repeated exposure to high concentrate of PAHs, especially semivolatile pyrene during 5–6 years of age and prenatal period, was associated with asthma in children [19]. Another study showed interaction of PAH exposure with secondhand tobacco smoke was associated with respiratory symptoms for children at age 12–24 months [8]. Studies investigated the effect of early repeated exposures to PAHs suggested that exposure to non-volatile PAHs enhanced allergic sensitization to cockroach allergen – a strong risk factor for greater asthma morbidity in children. In contrast, non-atopic children were susceptible to adverse respiratory effects due to pyrene, but not higher molecular weight (non-volatile) PAHs [20–22]. Another interesting research found that PAH exposure were associated with increased risk of new cockroach sensitization in 9 years old children in urban inner-city, which was a strong risk factor for urban asthma [23]. However, not all of the PAHs affect on respiratory health. Jung et al. found that while the effects of repeated high exposure to unsubstituted semivolatile PAHs (i.e. pyrene) may induce asthma, exposure to alkylated PAHs on respiratory health is more limited because alkylated PAHs opposed to parent PAHs [24]. Rosa et al. discovered that while combined prenatal exposure to PAH and environmental tobacco smoke (ETS) appears to be associated with asthma, exposure to PAH alone does not appear associated with asthma at age 5–6 years [25].

The potential mechanism for the association between PAHs and asthma has been proposed in some previous studies. The risk of asthma are supposed to be effected by PAHs and other anthropogenic oxidants through bronchial inflammation and bronchoconstriction [26]. Also PAHs are proved to have a well-established ability to produce reactive oxygen species that can affect asthma

morbidity rate [27]. The exposure of pyrene led to up-regulation of the IL-4 promoter activity [28]. Li et al. have found that PAHs in diesel exhaust can induce a cascade of oxidative stress that result in airway inflammation [27,29]. One consequence of the PAH-enhance oxidative stress is the increased production of IgE [30]. PAHs could enhance allergic inflammation and stimulate inflammatory responses through the immunoglobulin E (IgE) pathway [30–32]. There also have study concluded that exposure to PAHs can induce epigenetic modification, and such modifications have been found to be associated with asthma [33].

Several *in vivo* and *in vitro* experimental findings also explain the underlying mechanism for the association between PAHs and asthma. *In vitro*, PAH was shown to increase IgE production through their effects on tensile B cells [34]. It could influence T-helper cell and B cell differentiation by skewing immune responses toward a Th2 specific profile, which favors B-cell production of IgE and eosinophils both of which are hallmarks of allergic asthma and allergic inflammation [35]. IL-17A has also been implicated as an important component of airway diseases including asthma and COPD as well as the rejection of lung transplants [36]. Plé et al. found that PAHs reciprocally regulated IL-17 and IL-22 in peripheral blood mononuclear cells in both healthy and asthmatic subjects through mechanisms involving both Aryl hydrocarbon Receptor(AhR)-dependent and -independent pathways [37]. The exposure to pyrene could enhance allergic IgE responses in mice [28,38]. Phillip et al. found that PAH impaired function of β -adrenergic receptors in murine tracheal epithelial cells and human airway smooth muscle cells [39]. One trial used ICR mice concluded that Asian sand dust-bound PAHs might contribute to the aggravation of lung eosinophilia [40]. Chu et al. using a novel chamber to determine the effects of a more physiological method of mouse exposure to ambient PAH, they found that prenatal exposure to PAH was associated with reduced β 2AR gene expression in the mouse lung, and postnatal exposure to PAH was borderline associated with increased airway hyper-reactivity [41]. Furthermore, many PAHs including pyrene, anthracene, benzo(a)-pyrene, fluoranthene and phenanthrene have been shown to increase IgE production, T helper 2 cytokine productions in rodent and studies that highlight the cellular influence of PAHs on the immune response and metabolism [37,42,43]. In another analysis of 256 Children's Health and

Table 3
Adjusted ORs (95% CIs) for the association between the quartiles of urinary polycyclic aromatic hydrocarbons and asthma or asthma symptom stratified by sex and age (6–12, 13–19).

Boy	6–12 years old			13–19 years old		
	Ever been told you have asthma	Coughing	Wheezing or whistling in chest	Ever been told you have asthma	Coughing	Wheezing or whistling in chest
1-naphthol						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.291(0.599–2.780)	0.886(0.194–4.048)	0.675(0.298–1.528)	1.086(0.547–2.155)	1.605(0.515–5.005)	1.764(0.835–3.728)
Q3	0.590(0.244–1.427)	0.421(0.083–2.139)	0.878(0.400–1.929)	0.807(0.397–1.641)	1.043(0.301–3.620)	1.808(0.874–3.741)
Q4	1.538(0.720–3.285)	0.873(0.192–3.970)	1.232(0.584–2.597)	1.164(0.611–1.216)	1.820(0.610–5.433)	1.549(0.750–3.200)
P for trend	0.053	0.128	0.425	0.461	0.899	0.304
2-naphthol						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	2.346(0.973–5.654)	0.997(0.185–5.374)	1.666(0.741–3.743)	1.612(0.833–3.117)	1.395(0.442–4.398)	1.914(0.936–3.917)
Q3	2.640(1.077–6.469)	3.439(0.783–15.105)	1.623(0.698–3.775)	1.165(0.574–2.368)	2.838(0.942–8.550)	1.506(0.717–3.162)
Q4	2.528(1.034–6.182)	1.144(0.210–6.228)	1.897(0.838–4.296)	1.079(0.532–2.189)	1.284(0.363–4.541)	1.392(0.659–2.939)
P for trend	0.253	0.037	0.397	0.411	0.821	0.487
3-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.917(0.542–1.551)	0.646(0.220–1.902)	0.701(0.395–1.242)	1.001(0.582–1.721)	1.110(0.468–2.629)	1.347(0.737–2.461)
Q3	0.556(0.312–0.993)	0.387(0.121–1.241)	0.639(0.358–1.142)	1.264(0.738–2.167)	1.009(0.398–2.555)	1.674(0.917–3.057)
Q4	1.020(0.593–1.754)	1.071(0.393–2.917)	1.101(0.630–1.921)	1.199(0.725–1.982)	1.380(0.603–3.159)	1.566(0.888–2.761)
P for trend	0.360	0.375	0.086	0.042	0.917	0.316
2-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.660(0.764–3.605)	0.115(0.011–1.234)	1.059(0.485–2.310)	1.068(0.535–2.134)	4.211(1.133–15.650)	1.378(0.670–2.832)
Q3	0.876(0.371–2.071)	0.827(0.197–3.463)	0.708(0.302–1.658)	1.598(0.796–3.208)	2.447(0.557–10.749)	2.470(1.223–4.988)
Q4	1.469(0.665–3.248)	0.769(0.179–3.296)	1.616(0.767–3.402)	1.237(0.622–2.459)	3.138(0.797–12.355)	1.068(0.503–2.268)
P for trend	0.963	0.697	0.270	0.058	0.709	0.381
3-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.794(0.354–1.783)	2.247(0.232–21.725)	1.045(0.455–2.403)	1.021(0.514–2.026)	0.697(0.228–2.129)	1.499(0.720–3.123)
Q3	0.943(0.421–2.113)	1.577(0.146–17.002)	0.789(0.321–1.940)	1.091(0.548–2.172)	1.149(0.417–3.161)	1.939(0.950–3.956)
Q4	0.957(0.437–2.094)	3.757(0.431–32.773)	1.646(0.746–3.629)	1.703(0.866–3.349)	1.058(0.344–3.258)	1.567(0.732–3.358)
P for trend	0.785	0.913	0.986	0.061	0.735	0.294
1-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	2.205(1.031–4.718)	2.671(0.272–26.215)	1.379(0.631–3.013)	0.919(0.467–1.808)	1.911(0.621–5.882)	1.180(0.584–2.382)
Q3	0.515(0.194–1.373)	2.831(0.295–27.196)	0.729(0.303–1.757)	1.159(0.589–2.279)	2.234(0.698–7.149)	1.502(0.745–3.031)
Q4	1.643(0.758–3.558)	4.794(0.550–41.806)	1.797(0.848–3.806)	1.513(0.795–2.876)	2.529(0.812–7.873)	1.588(0.805–3.132)
P for trend	0.196	0.201	0.064	0.039	0.453	0.096
2-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.753(0.842–3.651)	0.453(0.066–3.115)	1.681(0.764–3.698)	1.028(0.479–2.205)	1.110(0.334–3.690)	1.371(0.628–2.993)
Q3	0.651(0.269–1.576)	1.093(0.198–6.038)	1.382(0.606–3.149)	1.806(0.884–3.691)	2.278(0.731–7.096)	2.653(1.286–5.474)
Q4	1.305(0.613–2.778)	2.542(0.592–10.917)	1.699(0.774–3.729)	2.353(1.156–4.792)*	1.552(0.467–5.159)	1.433(0.639–3.211)
P for trend	0.628	0.226	0.598	0.021*	0.844	0.189
1-pyrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.106(0.472–2.592)	3.390(0.581–19.779)	0.566(0.243–1.316)	0.718(0.345–1.494)	0.950(0.301–2.997)	1.303(0.633–2.682)
Q3	0.791(0.344–1.817)	0.470(0.058–3.803)	0.650(0.305–1.384)	1.725(0.913–3.260)	1.903(0.682–5.311)	2.065(1.048–4.071)
Q4	1.377(0.621–3.053)	2.139(0.378–12.114)	0.823(0.384–1.762)	1.469(0.775–2.785)	1.957(0.679–5.638)	1.594(0.796–3.190)
P for trend	0.456	0.096	0.189	0.160	0.265	0.202
9-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.434(0.553–3.719)	1.395(0.201–9.691)	1.441(0.548–3.786)	1.328(0.519–3.402)	3.035(0.467–19.729)	2.194(0.817–5.894)
Q3	0.803(0.264–2.440)	0.649(0.078–5.415)	0.781(0.255–2.394)	1.754(0.742–4.147)	3.105(0.526–18.326)	2.449(0.941–6.376)
Q4	1.624(0.641–4.117)	2.714(0.451–16.340)	1.351(0.516–3.538)	1.593(0.643–3.949)	2.708(0.414–17.720)	1.757(0.647–4.771)
P for trend	0.170	0.432	0.110	0.161	0.886	0.308
4-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.442(0.144–1.359)	N/A	0.759(0.223–2.579)	N/A	2.453(0.366–16.433)	1.596(0.617–4.129)
Q3	0.463(0.155–1.386)	N/A	1.153(0.376–3.529)	N/A	2.322(0.358–15.073)	1.749(0.652–4.689)
Q4	0.668(0.233–1.918)	N/A	0.940(0.289–3.056)	N/A	3.024(0.503–18.168)	0.984(0.352–2.752)
P for trend	0.748	N/A	0.429	N/A	0.715	0.489
Girl	6–12 years old			13–19 years old		
	Ever been told you have asthma	Coughing	Wheezing or whistling in chest	Ever been told you have asthma	Coughing	Wheezing or whistling in chest
1-naphthol						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.540(0.743–3.191)	0.330(0.081–1.343)	0.575(0.241–1.369)	0.692(0.350–1.368)	1.379(0.388–4.898)	0.736(0.384–1.409)
Q3	1.614(0.798–3.265)	0.562(0.171–1.846)	1.290(0.631–2.637)	0.841(0.413–1.709)	1.764(0.483–6.438)	1.159(0.609–2.206)
Q4	0.946(0.403–2.224)	0.476(0.118–1.922)	1.913(0.910–4.020)	1.207(0.639–2.281)	1.663(0.440–6.282)	1.198(0.647–2.216)
P for trend	0.768	0.767	0.944	0.683	0.582	0.573

Table 3 (continued)

2-naphthol						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.550(0.749–3.208)	0.440(0.132–1.467)	1.162(0.531–2.543)	1.488(0.687–3.226)	1.037(0.333–3.225)	1.121(0.549–2.287)
Q3	1.248(0.589–2.644)	0.298(0.072–1.244)	1.388(0.640–3.009)	2.203(1.071–4.529)	0.950(0.292–3.091)	1.430(0.736–2.778)
Q4	1.184(0.529–2.650)	0.430(0.099–1.870)	1.600(0.711–3.599)	1.862(0.919–3.771)	0.837(0.254–2.757)	1.518(0.803–2.868)
P for trend	0.728	0.930	0.781	0.136	0.205	0.184
3-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.151(0.665–1.992)	0.677(0.277–1.653)	0.918(0.500–1.685)	0.964(0.593–1.566)	0.565(0.238–1.341)	1.012(0.617–1.661)
Q3	1.039(0.610–1.771)	0.473(0.203–1.101)	1.195(0.687–2.078)	0.789(0.460–1.352)	0.725(0.310–1.692)	1.054(0.627–1.771)
Q4	1.310(0.742–2.311)	0.272(0.084–0.883)	1.431(0.792–2.587)	1.031(0.634–1.674)	0.689(0.300–1.583)	1.326(0.826–2.130)
P for trend	0.063	0.165	0.043	0.238	0.337	0.620
2-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.859(0.377–1.957)	1.534(0.431–5.457)	0.915(0.383–2.183)	1.072(0.555–2.070)	1.016(0.361–2.857)	0.971(0.516–1.829)
Q3	1.015(0.487–2.118)	0.651(0.178–2.376)	0.971(0.437–2.155)	1.418(0.747–2.690)	0.252(0.052–1.221)	1.140(0.609–2.133)
Q4	1.282(0.606–2.713)	0.294(0.053–1.650)	1.852(0.854–4.015)	0.958(0.477–1.925)	1.004(0.359–2.806)	1.313(0.707–2.439)
P for trend	0.625	0.195	0.058	0.326	0.308	0.520
3-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.755(0.317–1.798)	0.735(0.208–2.601)	1.572(0.647–3.816)	0.718(0.377–1.367)	0.444(0.144–1.365)	0.755(0.407–1.400)
Q3	1.701(0.797–3.629)	0.190(0.040–0.901)	1.622(0.687–3.829)	1.105(0.578–2.111)	0.672(0.230–1.963)	0.944(0.496–1.799)
Q4	0.912(0.412–2.016)	0.405(0.109–1.507)	1.424(0.605–3.354)	0.991(0.503–1.951)	0.657(0.211–2.048)	1.560(0.854–2.852)
P for trend	0.820	0.638	0.075	0.950	0.493	0.986
1-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.008(0.439–2.315)	0.414(0.110–1.561)	0.658(0.278–1.559)	0.950(0.491–1.841)	0.777(0.233–2.589)	1.408(0.737–2.688)
Q3	0.869(0.393–1.923)	0.326(0.091–1.170)	0.655(0.293–1.465)	0.940(0.452–1.952)	1.778(0.586–5.396)	1.251(0.613–2.552)
Q4	1.399(0.655–2.986)	0.278(0.073–1.057)	1.171(0.550–2.494)	1.413(0.726–2.748)	1.022(0.305–3.421)	1.865(0.964–3.610)
P for trend	0.072	0.494	0.160	0.911	0.499	0.823
2-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.435(0.634–3.245)	0.550(0.143–2.125)	1.110(0.487–2.528)	0.868(0.437–1.725)	0.657(0.205–2.112)	1.216(0.614–2.307)
Q3	2.012(0.919–4.405)	0.931(0.267–3.247)	1.533(0.697–3.373)	1.416(0.747–2.686)	0.925(0.323–2.650)	1.280(0.674–2.431)
Q4	1.520(0.686–3.367)	0.325(0.076–1.398)	1.241(0.562–2.737)	1.205(0.607–2.392)	0.963(0.311–2.986)	1.552(0.810–2.974)
P for trend	0.740	0.956	0.835	0.950	0.777	0.809
1-pyrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	2.560(0.964–6.800)	0.717(0.170–3.028)	0.636(0.276–1.463)	1.327(0.688–2.563)	0.874(0.310–2.468)	1.334(0.696–2.557)
Q3	2.452(0.936–6.425)	0.776(0.174–3.460)	0.644(0.288–1.443)	1.583(0.793–3.162)	0.930(0.261–3.312)	2.041(1.062–3.921)
Q4	2.090(0.792–5.518)	1.045(0.266–4.115)	0.888(0.410–1.924)	1.300(0.626–2.702)	1.423(0.471–4.297)	1.693(0.848–3.380)
P for trend	0.354	0.675	0.121	0.191	0.517	0.058
9-fluorene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.860(0.722–4.791)	0.593(0.129–2.731)	0.588(0.209–1.649)	1.581(0.683–3.661)	0.831(0.164–4.218)	1.233(0.511–2.975)
Q3	1.296(0.487–3.449)	0.426(0.082–2.202)	1.201(0.476–3.030)	1.892(0.801–4.470)	1.555(0.364–6.635)	2.059(0.885–4.790)
Q4	0.852(0.288–2.519)	0.146(0.014–1.550)	0.469(0.156–1.414)	1.080(0.436–2.678)	0.827(0.187–3.662)	1.633(0.694–3.843)
P for trend	0.747	0.412	0.768	0.389	0.887	0.043
4-phenanthrene						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1.314(0.481–3.590)	1.079(0.151–7.720)	0.666(0.220–2.022)	1.836(0.690–4.882)	0.720(0.105–4.959)	3.707(1.183–11.612)
Q3	1.136(0.396–3.259)	3.524(0.442–28.122)	0.814(0.266–2.489)	0.812(0.281–2.349)	2.412(0.414–14.060)	2.743(0.863–8.723)
Q4	0.802(0.277–2.319)	0.333(0.023–4.736)	0.918(0.317–2.662)	2.026(0.783–5.244)	0.828(0.117–5.853)	4.086(1.326–12.584)*
P for trend	0.468	0.802	0.711	0.601	0.597	0.043*

OR were adjusted for age (years), race (Mexican-American, other Hispanic, non-Hispanic White, non-Hispanic Black, and Other Race-including multi-racial).

PIR (tertiles), BMI (tertiles), and gender.

*Statistically significant ($p < 0.05$).

N/A: the sample is too small to get the OR.

Air Pollution Study (CHAPS) subjects, the results indicated that increased ambient PAH exposure significantly impaired systemic immunity and epigenetic modifications in two key genes involved in atopy: FoxP3 and IFN γ , with a higher influence on atopic children [44].

To our knowledge, it was the only investigation of asthma in children related to urinary PAHs in the United States and adds to a worldwide literature on this topic. However, some limitations still lies in our study. First, although we adjusted for potential confounders, some confounders such as cotinine and education were not recorded allowing for the adjustment in this analysis. Secondly, because the study was cross-sectional, it is not possible to know whether PAHs enhanced the risk of asthma or asthma symptom.

5. Conclusion

The study is a cross-sectional case–control study of 500 children aged 3–5 years from Odense, Denmark.

In summary, our study indicated that urinary PAHs was positive associated with asthma or asthma symptom among children age 6–19 years. Although the exact mechanism of how PAHs contributes to asthma has not been fully elucidated, our results may contribute to a better understanding of asthma from an epidemiological standpoint. Age of 6–19 years are important time windows for the developing of asthma or asthma symptoms. Further researches exploring the specific interventions to reduce PAH exposure could be beneficial to diminish the risk of developing asthma among young children.

Table 4

Adjusted ORs (95% CIs) for asthma and asthma related symptoms by exposure quartiles of urinary polycyclic aromatic hydrocarbons.

	Ever been told you have asthma	Coughing	Wheezing or whistling in chest
1-naphthol			
Q1	Reference	Reference	Reference
Q2	1.061(0.749–1.504)	0.919(0.501–1.688)	0.836(0.577–1.211)
Q3	0.903(0.629–1.296)	0.854(0.459–1.586)	1.181(0.833–1.676)
Q4	1.248(0.884–1.763)	1.131(0.617–2.076)	1.397(0.990–1.970)
P for trend	0.645	0.809	0.516
2-naphthol			
Q1	Reference	Reference	Reference
Q2	1.611(1.118–2.321)	0.958(0.526–1.744)	1.350(0.935–1.950)
Q3	1.584(1.095–2.290)	1.351(0.754–2.421)	1.450(1.005–2.091)
Q4	1.466(1.011–2.126)	0.859(0.448–1.645)	1.526(1.061–2.193)
P for trend	0.898	0.829	0.819
3-fluorene			
Q1	Reference	Reference	Reference
Q2	1.001(0.772–1.297)	0.729(0.467–1.138)	0.966(0.730–1.277)
Q3	0.879(0.671–1.150)	0.644(0.409–1.014)	1.080(0.819–1.425)
Q4	1.122(0.868–1.450)	0.765(0.492–1.190)	1.328(1.017–1.734)
P for trend	0.015	0.598	0.084
2-fluorene			
Q1	Reference	Reference	Reference
Q2	1.098(0.769–1.569)	1.462(0.807–2.648)	1.024(0.713–1.470)
Q3	1.207(0.846–1.722)	0.894(0.467–1.713)	1.186(0.830–1.695)
Q4	1.195(0.837–1.706)	1.078(0.581–2.000)	1.414(0.998–2.003)
P for trend	0.065	0.429	0.084
3-phenanthrene			
Q1	Reference	Reference	Reference
Q2	0.857(0.597–1.231)	0.747(0.408–1.368)	1.126(0.783–1.618)
Q3	1.186(0.838–1.679)	0.750(0.409–1.376)	1.233(0.856–1.777)
Q4	1.127(0.791–1.605)	0.880(0.486–1.596)	1.544(1.082–2.205)
P for trend	0.711	0.432	0.193
1-phenanthrene			
Q1	Reference	Reference	Reference
Q2	1.121(0.788–1.593)	1.094(0.582–2.056)	1.157(0.806–1.660)
Q3	0.845(0.579–1.233)	1.326(0.713–2.466)	0.997(0.683–1.455)
Q4	1.411(1.022–2.031)	1.248(0.670–2.322)	1.651(1.165–2.340)
P for trend	0.053	0.802	0.076
2-phenanthrene			
Q1	Reference	Reference	Reference
Q2	1.192(0.828–1.716)	0.784(0.414–1.488)	1.310(0.907–1.893)
Q3	1.392(0.973–1.933)	1.270(0.708–2.281)	1.656(1.158–2.369)
Q4	1.521(1.063–2.175)	1.089(0.598–1.986)	1.496(1.035–2.162)
P for trend	0.091	0.968	0.232
1-pyrene			
Q1	Reference	Reference	Reference
Q2	1.233(0.854–1.781)	1.211(0.666–2.205)	0.973(0.675–1.403)
Q3	1.406(0.977–2.024)	1.020(0.534–1.950)	1.278(0.897–1.821)
Q4	1.444(1.003–2.080)*	1.588(0.874–2.886)	1.282(0.897–1.832)
P for trend	0.039*	0.229	0.002
9-fluorene			
Q1	Reference	Reference	Reference
Q2	1.476(0.945–2.305)	1.248(0.549–2.836)	1.260(0.793–2.002)
Q3	1.400(0.888–2.206)	1.084(0.476–2.469)	1.563(0.994–2.459)
Q4	1.263(0.794–2.010)	1.332(0.598–2.970)	1.374(0.863–2.188)
P for trend	0.046	0.995	0.037
4-phenanthrene			
Q1	Reference	Reference	Reference
Q2	1.118(0.698–1.791)	1.315(0.492–3.515)	1.430(0.853–2.397)
Q3	0.911(0.556–1.493)	2.280(0.919–5.659)	1.555(0.928–2.606)
Q4	1.020(0.633–1.642)	1.618(0.641–4.087)	1.466(0.876–2.453)
P for trend	0.749	0.828	0.027

OR were adjusted for age (years), race (Mexican-American, other Hispanic, non-Hispanic White, non-Hispanic Black, and Other Race-including multi-racial), PIR (tertiles), BMI (tertiles), and gender.

*Statistically significant ($p < 0.05$).

Conflict of interest statement

No.

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References

- [1] E.P. Brigham, M.C. McCormack, C.M. Takemoto, E.C. Matsui, Iron status is associated with asthma and lung function in US women, *PLoS One* 10 (2015) e0117545.
- [2] L.J. Akinbami, J.E. Moorman, P.L. Garbe, E.J. Sondik, Status of childhood asthma in the United States, 1980–2007, *Pediatrics* 123 (Suppl. 3) (2009) S131–S145.
- [3] S.W. Nicholas, B. Jean-Louis, B. Ortiz, M. Northridge, K. Shoemaker, R. Vaughan, et al., Addressing the childhood asthma crisis in Harlem: the Harlem Children's Zone Asthma Initiative, *Am. J. Public Health* 95 (2005) 245–249.
- [4] C. Almqvist, M. Worm, B. Leynaert, Impact of gender on asthma in childhood and adolescence: a GA2LEN review, *Allergy* 63 (2008) 47–57.
- [5] P. Karimi, K.O. Peters, K. Bidad, P.T. Strickland, Polycyclic aromatic hydrocarbons and childhood asthma, *Eur. J. Epidemiol.* 30 (2015) 91–101.
- [6] H.C. Brandt, W.P. Watson, Monitoring human occupational and environmental exposures to polycyclic aromatic compounds, *Ann. Occup. Hyg.* 47 (2003) 349–378.
- [7] H.A. Jeng, C.H. Pan, N. Diawara, G.P. Chang-Chien, W.Y. Lin, C.T. Huang, et al., Polycyclic aromatic hydrocarbon-induced oxidative stress and lipid peroxidation in relation to immunological alteration, *Occup. Environ. Med.* 68 (2011) 653–658.
- [8] R.L. Miller, R. Garfinkel, M. Horton, D. Camann, F.P. Perera, R.M. Whyatt, et al., Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort, *Chest* 126 (2004) 1071–1078.
- [9] J. Liu, L. Zhang, L.C. Winterroth, M. Garcia, S. Weiman, J.W. Wong, et al., Epigenetically mediated pathogenic effects of phenanthrene on regulatory T cells, *J. Toxicol.* 2013 (2013) 967029.
- [10] W. Jedrychowski, A. Galas, A. Pac, E. Flak, D. Camman, V. Rauh, et al., Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life, *Eur. J. Epidemiol.* 20 (2005) 775–782.
- [11] F.P. Perera, V. Rauh, R.M. Whyatt, W.Y. Tsai, D. Tang, D. Diaz, et al., Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children, *Environ. Health Perspect.* 114 (2006) 1287–1292.
- [12] A.M. Padula, J.R. Balmes, E.A. Eisen, J. Mann, E.M. Noth, F.W. Lurmann, et al., Ambient polycyclic aromatic hydrocarbons and pulmonary function in children, *J. Expo. Sci. Environ. Epidemiol.* 25 (2015) 295–302.
- [13] S.L. Gale, E.M. Noth, J. Mann, J. Balmes, S.K. Hammond, I.B. Tager, Polycyclic aromatic hydrocarbon exposure and wheeze in a cohort of children with asthma in Fresno, CA, *J. Expo. Sci. Environ. Epidemiol.* 22 (2012) 386–392.
- [14] N.M. Al-Daghiri, M.S. Alokail, S.H. Abd-Alrahman, H.M. Draz, S.M. Yakout, M. Clerici, Polycyclic aromatic hydrocarbon exposure and pediatric asthma in children: a case-control study, *Environ. Health* 12 (2013) 1.
- [15] G. Zipf, M. Chiappa, K.S. Porter, Y. Ostchega, B.G. Lewis, J. Dostal, National health and nutrition examination survey: plan and operations, 1999–2010, *Vital Health Stat.* 1 (2013) 1–37.
- [16] S.E. Barlow, Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report, *Pediatrics* 120 (Suppl. 4) (2007) S164–S192.
- [17] Y. Ma, S. Harrad, Spatiotemporal analysis and human exposure assessment on polycyclic aromatic hydrocarbons in indoor air, settled house dust, and diet: a review, *Environ. Int.* 84 (2015) 7–16.
- [18] Y. Yu, X. Wang, B. Wang, S. Tao, W. Liu, J. Cao, et al., Polycyclic aromatic hydrocarbon residues in human milk, placenta, and umbilical cord blood in Beijing, China, *Environ. Sci. Technol.* 45 (2011) 10235–10242.
- [19] K.H. Jung, B. Yan, K. Moors, S.N. Chillrud, M.S. Perzanowski, R.M. Whyatt, et al., Repeated exposure to polycyclic aromatic hydrocarbons and asthma: effect of serotopy, *Ann. Allergy Asthma Immunol.* 109 (2012) 249–254.
- [20] R.L. Miller, R. Garfinkel, C. Lendor, L. Hoepner, Z. Li, L. Romanoff, et al., Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner-city cohort, *Pediatr. Allergy Immunol.* 21 (2010) 260–267.
- [21] P. Karimi, S.Z. Modarresi, M.A. Sahraian, R. Shokouhi Shoormasti, M. Mahlooji, A. Kazemnejad, et al., The relation of multiple sclerosis with allergy and atopy: a case control study, *Iran. J. Allergy Asthma Immunol.* 12 (2013) 182–189.
- [22] M.S. Perzanowski, G.L. Chew, A. Divjan, K.H. Jung, R. Ridder, D. Tang, et al., Early-life cockroach allergen and polycyclic aromatic hydrocarbon exposures predict cockroach sensitization among inner-city children, *J. Allergy Clin. Immunol.* 131 (2013) 886–893.
- [23] K.H. Jung, S. Lovinsky-Desir, M. Perzanowski, X. Liu, C. Maher, E. Gil, et al., Repeatedly high polycyclic aromatic hydrocarbon exposure and cockroach sensitization among inner-city children, *Environ. Res.* 140 (2015) 649–656.
- [24] K.H. Jung, M. Perzanowski, A. Rundle, K. Moors, B. Yan, S.N. Chillrud, et al., Polycyclic aromatic hydrocarbon exposure, obesity and childhood asthma in an urban cohort, *Environ. Res.* 128 (2014) 35–41.
- [25] M.J. Rosa, K.H. Jung, M.S. Perzanowski, E.A. Kelvin, K.W. Darling, D.E. Camann, et al., Prenatal exposure to polycyclic aromatic hydrocarbons, environmental tobacco smoke and asthma, *Respir. Med.* 105 (2011) 869–876.
- [26] W. Jedrychowski, F.P. Perera, R. Whyatt, E. Mroz, E. Flak, R. Jacek, et al., Wheezing and lung function measured in subjects exposed to various levels of fine particles and polycyclic aromatic hydrocarbons, *Central Eur. J. Med.* 2 (2007) 66–78.
- [27] A.E. Nel, D. Diaz-Sanchez, N. Li, The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress, *Curr. Opin. Pulm. Med.* 7 (2001) 20–26.
- [28] H. Bommel, M. Li-Weber, E. Serfling, A. Duschl, The environmental pollutant pyrene induces the production of IL-4, *J. Allergy Clin. Immunol.* 105 (2000) 796–802.
- [29] N. Li, C. Sioutas, A. Cho, D. Schmitz, C. Misra, J. Sempf, et al., Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage, *Environ. Health Perspect.* 111 (2003) 455–460.
- [30] A.E. Nel, D. Diaz-Sanchez, D. Ng, T. Hiura, A. Saxon, Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system, *J. Allergy Clin. Immunol.* 102 (1998) 539–554.
- [31] A. Tsien, D. Diaz-Sanchez, J. Ma, A. Saxon, The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances IgE production by IgE-secreting EBV-transformed human B cells in vitro, *Toxicol. Appl. Pharmacol.* 142 (1997) 256–263.
- [32] S. Lubitz, W. Schober, G. Pusch, R. Effner, N. Klopp, H. Behrendt, et al., Polycyclic aromatic hydrocarbons from diesel emissions exert proallergic effects in birch pollen allergic individuals through enhanced mediator release from basophils, *Environ. Toxicol.* 25 (2010) 188–197.
- [33] E.C. Klingbeil, K.M. Hew, U.C. Nygaard, K.C. Nadeau, Polycyclic aromatic hydrocarbons, tobacco smoke, and epigenetic remodeling in asthma, *Immunol. Res.* 58 (2014) 369–373.
- [34] H. Takenaka, K. Zhang, D. Diaz-Sanchez, A. Tsien, A. Saxon, Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production, *J. Allergy Clin. Immunol.* 95 (1995) 103–115.
- [35] M.A. Riedl, A.E. Nel, Importance of oxidative stress in the pathogenesis and treatment of asthma, *Curr. Opin. Allergy Clin. Immunol.* 8 (2008) 49–56.
- [36] M. Van Voorhis, S. Knopp, W. Julliard, J.H. Fechner, X. Zhang, J.J. Schauer, et al., Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor, *PLoS One* 8 (2013) e82545.
- [37] C. Ple, Y. Fan, S. Ait Yahia, H. Vorng, L. Everaere, C. Chenivesse, et al., Polycyclic aromatic hydrocarbons reciprocally regulate IL-22 and IL-17 cytokines in peripheral blood mononuclear cells from both healthy and asthmatic subjects, *PLoS One* 10 (2015) e0122372.
- [38] T. Kanoh, T. Suzuki, M. Ishimori, S. Ikeda, M. Ohasawa, H. Ohkuni, et al., Adjuvant activities of pyrene, anthracene, fluoranthene and benzo(a)pyrene in production of anti-IgE antibody to Japanese cedar pollen allergen in mice, *J. Clin. Lab. Immunol.* 48 (1996) 133–147.
- [39] P. Factor, A.T. Akhmedov, J.D. McDonald, A. Qu, J. Wu, H. Jiang, et al., Polycyclic aromatic hydrocarbons impair function of beta2-adrenergic receptors in airway epithelial and smooth muscle cells, *Am. J. Respir. Cell Mol. Biol.* 45 (2011) 1045–1049.
- [40] Y. Ren, T. Ichinose, M. He, K. Arashidani, Y. Yoshida, S. Yoshida, et al., Aggravation of ovalbumin-induced murine asthma by co-exposure to desert-dust and organic chemicals: an animal model study, *Environ. Health* 13 (2014) 83.
- [41] S. Chu, H. Zhang, C. Maher, J.D. McDonald, X. Zhang, S.M. Ho, et al., Prenatal and postnatal polycyclic aromatic hydrocarbon exposure, airway hyperreactivity, and Beta-2 adrenergic receptor function in sensitized mouse offspring, *J. Toxicol.* 2013 (2013) 603581.
- [42] H. Takano, T. Yoshikawa, T. Ichinose, Y. Miyabara, K. Imaoka, M. Sagai, Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice, *Am. J. Respir. Crit. Care Med.* 156 (1997) 36–42.
- [43] H. Fujimaki, F. Shiraishi, Y. Aoki, K. Saneyoshi, Modulated cytokine production from cervical lymph node cells treated with B[a]P and PCB, *Chemosphere* 34 (1997) 1487–1493.
- [44] K.M. Hew, A.I. Walker, A. Kohli, M. Garcia, A. Syed, C. McDonald-Hyman, et al., Childhood exposure to ambient polycyclic aromatic hydrocarbons is linked to epigenetic modifications and impaired systemic immunity in T cells, *Clin. Exp. Allergy* 45 (2015) 238–248.