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REVIEW

Polycyclic aromatic hydrocarbons and childhood asthma

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Abstract Asthma is the most common chronic illness in children living in developed countries and the leading cause of childhood hospitalization and school absenteeism. Prevalence rates of asthma are increasing and show disparities across gender, geographic regions, and ethnic/racial groups. Common risk factors for developing childhood asthma include exposure to tobacco smoke, previous allergic reactions, a family history of asthma, allergic rhinitis or eczema, living in an urban environment, obesity and lack of physical exercise, severe lower respiratory tract infections, and male gender. Asthma exacerbation in children can be triggered by a variety of factors, including allergens (e.g., pollen, dust mites, and animal dander), viral and bacterial infections, exercise, and exposure to airway irritants. Recent studies have shown that exposure to polycyclic aromatic hydrocarbons (PAHs), a major component of fine particulate matter from combustion sources, is also associated with onset of asthma, and increasing asthmatic symptoms. In this paper, we review sources of childhood PAH exposure and the association between airborne PAH exposure and childhood asthma prevalence and exacerbation.

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Childhood asthma

Incidence, prevalence, and morbidity

Childhood asthma is a chronic and heterogeneous disease characterized by recurrent airway obstruction, bronchial hyper-responsiveness, and airway inflammation [1]. It is the most common chronic illness in children, affecting approximately one in eight children worldwide, and 9.1 % (6.7 million children) in the United States (US) [2, 3]. Asthma is the leading cause of childhood hospitalization and school absenteeism among children around the world. Only in the US, it causes more than 10.5 million physician visits annually, and is projected to cost over 20 billion dollars in health expenditures and lost productivity [4, 5]. In the United Kingdom, 70 % of parents of asthmatic children take time off from work due to their child's asthma, while 13 % of them had given up their jobs completely [6].

Prevalence rates of asthma show disparities across gender, regions, and ethnic/racial groups. Asthma is more prevalent in boys, as 2/3 of children with asthma are males [7]. Asthma is most common in developed countries, however, it is becoming increasingly common in developing countries, which is most likely related to the increased urbanization of communities [6]. From 1950 to 2000, the prevalence of childhood asthma increased drastically in Europe, and then decreased during the last decade [8]. It varies across Europe from east to west, which is probably because of simultaneous changes in lifestyle in

eastern Europe [8]. The lowest prevalence is reported 1.6 % in Albania and the highest reported 20.7 % in the United Kingdom [9]. Furthermore, racial disparities in childhood asthma are extensive. African American children have 60 % higher asthma prevalence, and children of Native American and Alaskan decent have 25 % higher prevalence than White children. The difference in prevalence between African Americans and Whites has increased since 1980 [10]. Hispanic children have higher rates compared to Whites; and among Hispanics, Puerto Rican children have higher prevalence rates than Mexican–American children [9]. Asian children have the lowest prevalence among races in the US [11]. Regional differences in asthma prevalence in the US are also present. Prevalence is highest in the northeast, and ranges from 4.4 % in Utah and Nevada to 12.1 % in Massachusetts (Fig. 1) [3]. The intersection of socioeconomic status, race and urbanity also influence asthma morbidity, while children who live in low-socioeconomic urban environments experience significantly more asthma-associated morbidity [9].

Trends

Globally, childhood asthma prevalence has increased more than twofold, from 3.6 % in 1980 to 7.5 % in 1995 [12]. While some of the global increase may be due to changes in diagnostic practice, there is general agreement that it is a true phenomenon [13]. This trend seems to be associated with changes in lifestyle, which is supported by studies that show an increased prevalence of asthma among those who have moved from a traditional to a more westernized style of living [14, 15]. Between 1980 and 1996, asthma prevalence increased by an average of 4.6 % annually [16, 17]. After a redesign of the National Health Interview Survey (NHIS) in 1997, the trends in annual estimated lifetime asthma, current asthma and asthma attack prevalence level out [17–19]. Childhood asthma prevalence in the US, as estimated in the 2007 NHIS, remains at historically high levels (9.1 %) (Fig. 2). An analysis of the National Health and Nutrition Examination Survey II, has shown asthma to be associated with younger maternal age (relative odds (RO) = 1.4), residence in the city center (RO = 1.6), and family income (lowest vs. highest tertile, RO = 1.7), frequent wheeze associated with low birth weight (RO = 1.4), and skinfold thickness (RO = 1.6) [16]. These factors, however, do not explain racial disparities in asthma prevalence. Even after adjustment for environmental exposures, parental history, and demographic factors, African American children still had 1.6 times higher odds of asthma diagnosis compared to White children and are 2.5 times more likely to experience asthma-related emergency department visits and hospitalizations [3, 16].

Symptoms and mortality

Asthma is characterized by attacks or episodes of inflammation and narrowing of small pulmonary airways [18]. Symptoms can include dyspnea, frequent or intermittent cough (especially at night and after exercise or exposure to cold air), wheezing, and chest congestion or tightness [19]. Expiratory dyspnea is a common symptom characteristic of asthma attacks, however, inspiratory dyspnea may coexist as symptoms progress [20]. In general, asthma severity ranges from mild to severe and life-threatening attacks,

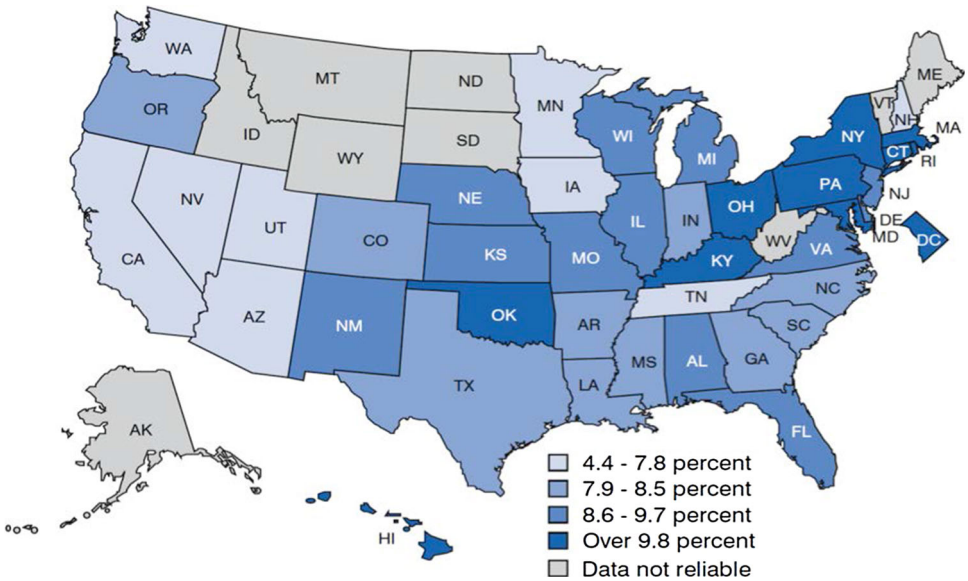

Fig. 1 Asthma prevalence among children 0–17 years old, by state, annual average for the period 2001–2005 [3]

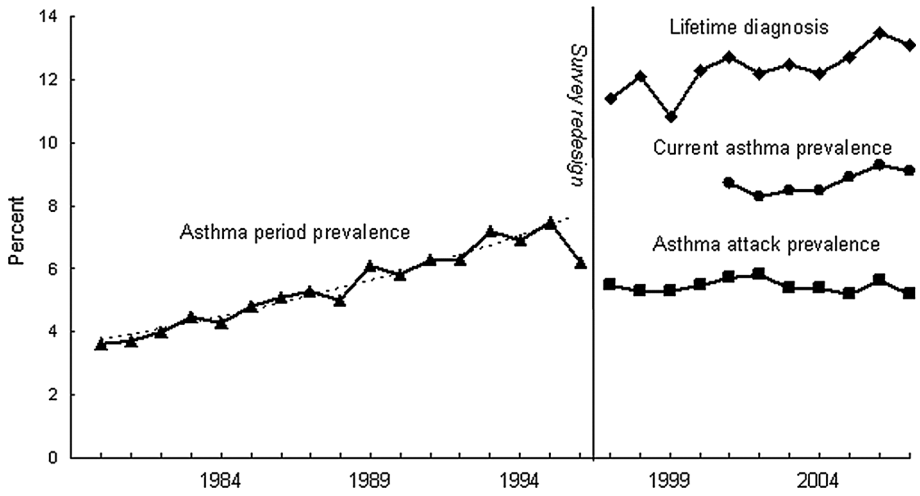

Fig. 2 Prevalence of asthma among children 0–17 years old in the United States, 1980–2007. In 1997, the NHIS survey was redesigned [17]

with children experiencing more severe symptoms than adults [3].

Asthma deaths among children are rare and potentially avoidable. High risk of asthma death is reported among children with severe, uncontrolled disease, a near-fatal attack of asthma, and a history of recurrent hospitalization or intubation for asthma [21]. Recent data from children aged 0–14 years revealed that mortality is generally very low in Europe, with little difference between countries, implying better control of the condition with improvements in treatment [22]. In 2005, 167 asthma-related deaths were reported among the US children (a mortality rate of 2.3 deaths per 1 million children) [12]. Asthma-related death rates increased by an average of 3.2 % per year from 1980 to 1996, then decreased by an average of 3.9 % per year from 1996 to 2005 [17]. Race and socioeconomic status are factors that confer higher rates of asthma-related mortality. African American children are 5 times more likely to die from asthma than White children [3]. Asthma-related mortality among African American children exceeds the expected difference based on racial disparities in prevalence, and may be related to other factors, such as access to care, exposure to smoking, and non-adherence to treatment among inner-city children [23]. In addition, children from low-socioeconomic families have dramatically higher overall mortality rates, compared to those from moderate/high-socioeconomic families [24].

Risk factors

Several factors have been associated with the development of childhood asthma, but none have proven to be an exclusive causative agent. Common risk factors that may increase the likelihood of developing childhood asthma include exposure to tobacco smoke, previous allergic reactions (allergic skin reactions, food allergies, or allergic rhinitis), a family history of asthma, allergic rhinitis or eczema, living in an urban environment, obesity and lack of physical exercise, severe lower respiratory tract infections (such as pneumonia), small family size, dietary habits, and male gender [25–33]. Other potential risk factors include peripheral blood eosinophilia, lower school-aged lung function, higher levels of airway responsiveness, and breast feeding [34, 35].

Asthma exacerbation or attacks in children is triggered by a variety of factors including allergens (e.g., pollen, dust mites, and animal dander), viral and bacterial infections, exercise, changes in the weather, and exposure to airway irritants (e.g., tobacco smoke) [36–42]. Recent studies have shown that exposure to polycyclic aromatic hydrocarbons (PAHs), a major component of fine particulate matter from combustion sources, is associated with onset of asthma, and increasing asthmatic symptoms [43, 44]. The aim of this paper is to review sources of childhood PAH exposure and the association between airborne PAH exposure and childhood asthma.

Polycyclic aromatic hydrocarbons (PAHs)

Characteristics

Polycyclic aromatic hydrocarbons (PAHs) are a group of hydrocarbons, defined by two or more fused aromatic rings, that are products of incomplete combustion of tobacco, wood, coal, and fossil fuels [45]. PAHs are one of the most widespread organic pollutants and the widespread environmental distribution of PAHs results in a great deal of human exposure [46, 47]. Due to their lipophilic nature, PAHs are easily absorbed and distributed throughout the human body

[48]. PAHs are metabolized by enzymes that convert xenobiotic compounds into more hydrophilic and polar metabolites for easier excretion in human body fluids [49]. There are hundreds of PAHs, which usually occur as complex mixtures rather than as individual compounds (Fig. 3) [50]. Volatile (e.g. naphthalene) and semi-volatile (e.g. phenanthrene and pyrene) PAHs are products of combustion at high temperatures, and can be found in both gas and solid phases [51, 52]. Non-volatile PAHs having 4–6 aromatic rings (e.g. benzo[a]nepyrene, benzo[a]anthracene and idenol[1,2,3,a,b]pyrene) are found as solids bound to particulate matter in air [52].

Sources of exposure

Humans are exposed to PAHs from occupational, environmental, medicinal and dietary sources. Routes of exposure include inhalation, ingestion or percutaneous penetration [53]. Volatile PAHs are primarily inhaled, while semi-volatile and non-volitile PAHs can be inhaled, ingested, and absorbed dermally [51, 52]. After absorption, PAHs distribute to various organs, especially the liver [54]. Initially, they are hydrophobic and relatively inert, but are metabolized within cells to many active forms, including diol-epoxides, quinones, semi-quinones and peroxides [50].

Diet

Diet is the main source of PAH exposure in non-smokers who are not occupationally exposed [55, 56]. The Total Human Environmental Exposure Study in the US estimated that diet accounts for up to 96 % of the daily intake of carcinogenic PAHs in non-smokers [57]. The highest levels of PAHs are found in diets including cereals, meat, and meat products and foods that are smoked, broiled, or grilled. Contamination of foods by PAHs may occur during food processing (e.g., smoking or cooking), or by accidental environmental contamination (e.g., atmospheric pollution of vegetables) [58, 59]. Agricultural crops can be an important source of exposure to PAHs due to the high surface area of some food plants that are exposed to atmospheric deposition of particulate matter containing PAHs [60, 61]. It is believed that the majority of PAH contamination of agricultural crops comes from the air rather than the soil [62].

Tobacco

Smoking tobacco is a major source of exposure to PAHs [63]. Several studies reported a significant positive relationship between urinary levels of the pyrene metabolite, 1-hydroxypyrene-glucuronide (1-OHPG) and smoking

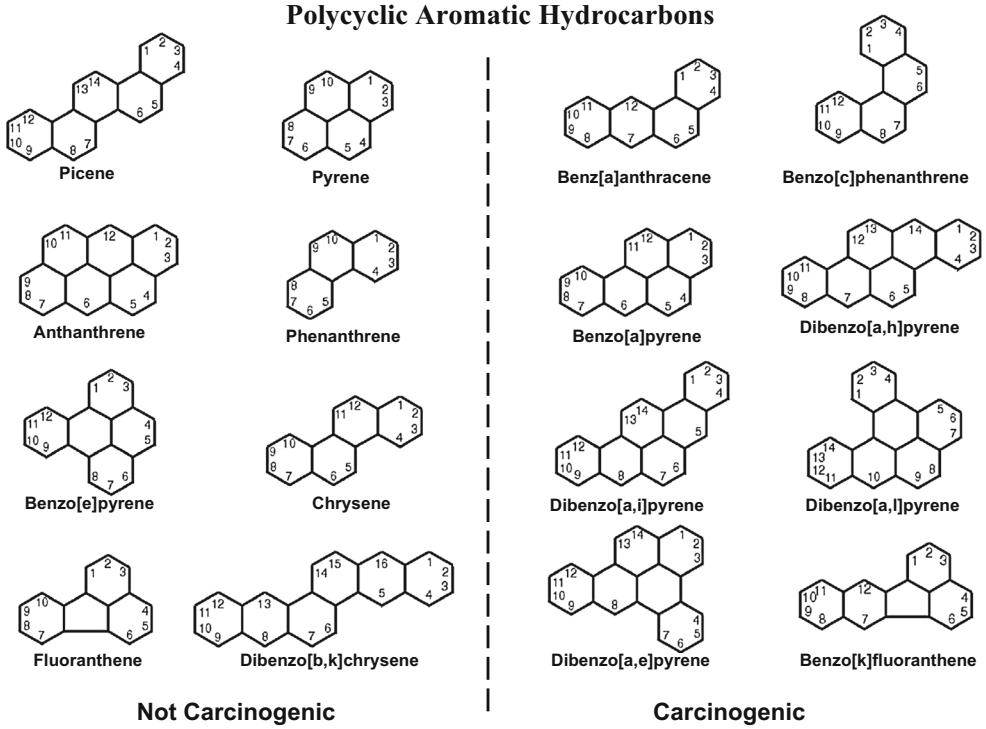

Fig. 3 Structures of common polycyclic aromatic hydrocarbons (PAHs). Source: Reprinted (adapted) with permission from Dipple, A. Polycyclic Aromatic Hydrocarbon Carcinogenesis. Polycyclic Hydrocarbons and Carcinogenesis. 1-17. Copyright (1985) American Chemical Society

[64, 65]. A study by Van Rooij et al. demonstrated that active smoking and PAH-containing food products account for 99 % of urinary excretion of PAH biomarkers in those with no other known exposure to PAHs [66]. Individuals in the US with recent smoking have significantly elevated levels of PAH metabolites in their urine compared to non-smokers [66]. Secondhand tobacco smoke exposure is also correlated with elevated urinary PAH metabolite concentration and children whose parents smoke at home have significantly elevated levels compared to children in non-smoking households [67, 68].

Occupation

Occupation is an important source of exposure to PAHs in a small portion of the population. The level of exposure to PAHs varies widely between occupations with high levels of exposure reported in chimney sweeps, foundry workers, blast furnace and coke-oven workers, vendors of broiled food, waste incineration, and steel plant workers [69–75]. The highest levels of exposure to PAHs occur in coke-oven, asphalt, and diesel workers [76, 77].

Indoor air pollution

Indoor air pollution consists of a complex mixture of agents penetrating from ambient (outdoor) air and agents generated by indoor sources [78]. The main source of indoor air PAHs is the combustion of solid fuels for cooking and heating. Smoking has been consistently described as a major source of indoor air pollution over the last several decades, with more than 30 % of all US children exposed to secondhand smoke [79]. It is estimated that children can spend as much as 90 % of their time indoors making them one of the most vulnerable groups to indoor air pollution exposures [80]. The major source of non-dietary PAH exposure in children is believed to be from indoor sources [81]. In contrast to outdoor environments, modifying indoor air PAHs is more achievable making indoor air pollution an attractive target for childhood asthma prevention [82].

Outdoor air pollution

Motor vehicle engine emissions are a major source of ambient PAHs, particularly in urban areas [83]. The highest PAH emission rates occur in diesel and gasoline engines operated without catalytic converters [84, 85]. In addition, industrial operations, waste incinerators, and residential boilers provide other major sources of ambient PAHs in urban areas [86]. According to the US Agency for Toxic Substances and Disease Registry (ATSDR), background atmospheric concentrations of representative PAHs vary from 0.02 to 1.2 ng/m3 in rural and 0.15–19.3 ng/m3 in urban areas [87]. Regulatory values range from 1 to 10 ng/m^3 in different countries, but are frequently exceeded in urban areas [48].

Measurement of PAH dose

A routine method for estimating dietary PAH dose is a combination of usual food intake information obtained from food frequency questionnaires (FFQ) and existing PAH residue databases (RD) containing mean concentrations of PAHs measured in cooked foods (FFQ-RD) [88, 89]. Benzo[a]pyrene is often used as a representative of the class of PAHs due to its carcinogenic potency, prevalence, and correlation with other PAHs [90]. The FFQ-RD method may improve accuracy compared with previously used surrogates of dietary PAH exposure, such as intake of meat or well-done meat [91]. However, there are still some limitations, including inaccurate reporting of usual intake and inadequacies (in completeness and accuracy) of the RD [88]. These limitations can potentially lead to measurement error in the dose and thus limit the power of studies to detect associations [92]. On the other hand, urinary biomarkers of PAH exposure present a practical alternative approach. For example, 1-hydroxypyrene-glucuronide (1-OHPG) is the major urinary metabolite of pyrene, a common PAH, and easily measured in human urine [93]. Since 1-OHPG occurs at higher concentration in urine than most other PAH exposure biomarkers, it has been proposed as a biomarker of exposure to PAHs [53]. The maximum concentration of 1-OHPG in human urine samples is usually found in the evening, suggesting this as a suitable time for sample collection for evaluation of PAHs [94]. Urinary 1-OHPG has also been demonstrated to be significantly higher in individuals exposed to high levels of PAH through their diet [95]. Urinary levels of metabolites of naphthalene (2-naphthol) and phenanthrene (3-hydroxyphenanthrene) have also been shown to be promising surrogates to assess PAH exposure [96]. The major metabolite of naphthalene, 2-naphthol, is primarily found in gas phase and is therefore as a good biomarker to assess airborne and occupational exposures to PAHs [54].

Health effects of PAHs

PAHs are significant components of PM2.5 (particulate matter diameter <2.5 μm) and less so of PM10 (<10 μm), both of which have been linked to adverse respiratory health [97]. In recent years, PAHs have received particular attention because of their oxidative potential and related cytotoxicity [98]. Exposure to PAHs has been linked to several adverse outcomes in children, including cognitive development, childhood IQ, and respiratory health [99–101]. The US National

Health and Nutrition Examination Survey (NHANES) (1999–2000, 2001–2002, and 2003–2004) provided comprehensive descriptions of reference ranges for a large panel of urinary PAH metabolites collected from a population of children and adults with no suspected occupational exposures [102, 103]. Higher level of PAHs was detected among children, suggesting that they may be at greater risk for adverse health effects [104].

PAHs are the principal carcinogenic chemical constituents in soot and coal tar that are responsible for cancer induction in animal models [50, 105, 106]. The International Agency for Research on Cancer (IARC) and the United States National Toxicology Program (NTP) have classified a number of PAHs as "known human carcinogens", "probable human carcinogens" or "reasonably anticipated to be a human carcinogen" The NTP lists 12 PAHs as human carcinogen, including benz[a]anthracene, *benzo[a]pyrene,* benzo[b]fluoranthene, benzo[j]fluoranthene, dibenz[a,h]anthracene, dibenzo[a,h]pyrene, dibenzo[a,i]-pyrene, indeno[1,2,3-cd]pyrene, benzo[k]fluoranthene, dibenzo[a,e]pyrene, dibenzo[a,l]pyrene, and 5-methylchrysene [107–109].

PAHs and childhood asthma

Several lines of evidence support an association between fine particulate matter, a major source of airborne PAHs, and childhood asthma. During the 2008 Beijing Olympics, the central government temporarily restricted air pollution emissions in Beijing, greatly reducing ambient pollutant levels. During this period, a statistically significant reduction in the mean concentration of PM2.5 (−27 %) coincided with a decrease in childhood asthma admissions [110]. In a prospective birth cohort study of 3,863 newborn children, outdoor PM2.5 levels were associated with a significant increase in the incidence of asthma (OR 1.28; 95 % CI 1.10–1.49), the prevalence of asthma (OR 1.26; 95 % CI 1.04–1.51), and the prevalence of asthma symptoms (OR 1.15; 95 % CI 1.02–1.28) [111].

Secondhand tobacco smoke is a major route of childhood PAH exposure and has been associated with childhood asthma. A meta-analysis of studies published from 1970 to 2005 showed a positive association between household secondhand tobacco smoke exposure and current childhood asthma (RR 1.25, 95 % CI 1.21–1.30), and incident childhood asthma (RR 1.21, 95 %CI 1.08–1.36) [112]. In addition, maternal tobacco smoking has been associated with an increased incidence of childhood asthma up to age 6 (OR 1.31, 95 %CI 1.22–1.41), but less strongly thereafter (OR 1.13, 95 %CI 1.04–1.22) [113]. Similarly, indoor air pollution has been associated with higher rates of reported childhood asthma; compared with other fuel types, coal was associated with the highest incidence of asthma [114–116].

Further studies suggest that specific components of PM2.5 including, black carbon, transition metals, or PAHs are associated with adverse respiratory outcomes and asthma, particularly in infants and children [101, 117–121]. Annual average particulate PAH exposure, estimated by a land use regression model, was associated with decreased forced expiratory volume (FEV1) in asthmatic children [122]. Miller et al. [123] reported an association between increased urinary PAH metabolites in children and biomarkers of pediatric allergy including anti-mouse IgE and/or anti-cat IgE levels. Subsequent studies investigated the effect of early repeated exposures to PAHs and reported that non-atopic children were susceptible to adverse respiratory effects due to pyrene, but not higher molecular weight (non-volatile) PAHs [123, 124]. In contrast, exposure to non-volatile PAHs enhanced allergic sensitization to cockroach allergen – a strong risk factor for greater asthma morbidity in children [125].

Studies suggest that PAHs may act through immunoglobulin E (IgE) to stimulate inflammatory responses and enhance allergic reactions [126–129]. Experimental evidence indicates that pyrene enhances allergic IgE responses in mice [130, 131]. Adjuvant effects of PAHs on IgE have been demonstrated in human nasal provocation studies. A study by Diaz-Sanchez et al. [133], showed that intranasal instillation of PAH rich diesel exhaust particles increased total IgE production, and acted as an adjuvant for ragweed specific IgE after challenges with both ragweed + DEP compared to ragweed alone [132, 133]. Exposures to PAHs in vivo may also influence B cell and T-helper 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 inflammation and allergic asthma [134]. Recent studies have focused on the role of PAHs on aryl hydrocarbon receptors (AHRs) and induction of Th17 cells. Th17 cells as a source of IL-17 and IL-22 are implicated in the pathogenesis of airway disease and particularly asthma [135, 136].

PAHs have also been linked to asthma through oxidative stress pathways (Fig. 4) [137–140]. PAHs bioactivated by cytochrome P450 generate reactive oxygen species (ROS) (e.g. epoxides, peroxides, semiquinones and quinones) that may enhance asthma morbidity [137]. Li et al. [141] demonstrated that PAHs in diesel exhaust can initiate a cascade of oxidative stress that leads to airway inflammation. In this model, the reactive oxygen species, from redox cycling of PAH intermediates, activate both the anti-inflammatory and the pro-inflammatory signaling pathways, leading to transcriptional upregulation of genes involved in regulating immune response

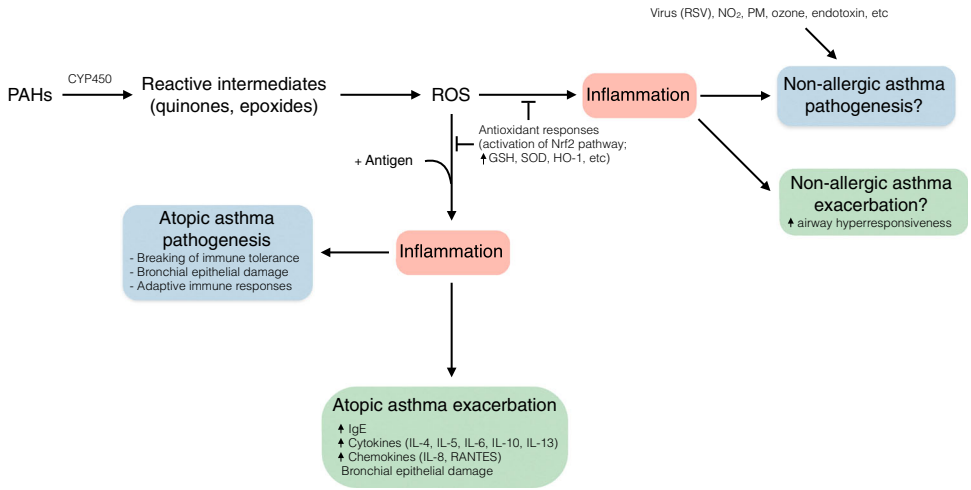

Fig. 4 PAH and asthma pathogenesis/exacerbation pathways. *CYP450* cytochrome P450, *GSH* glutathione, *HO-1* heme oxygenase 1, *IgE* immunoglobulin E, *IL* interleukin, NO_2 nitrogen dioxide, *Nrf2* nuclear factor (erythroid derived-2) like 2, *PM* particulate matter, *RANTES* regulated on activation, normal T cell expressed and secreted, *ROS* reactive oxygen species, *RSV* respiratory syncytial virus, *SOD* superoxide dismutase

[137, 142–144]. Immune responses include synthesis of cytokines, cell adhesion molecules and chemokines, increases in neutrophils, eosinophils, and macrophage production and activity, resulting in airway inflammation and asthma exacerbation [124, 137, 145]. Other studies suggest that prenatal exposure to PAHs may account for some of the observed increased asthma prevalence [146]. A recent prospective cohort study revealed that prenatal PAH exposure is associated with significant reduction in Forced Expiratory Volume in 0.5 s, Forced Expiratory Volume in 1 s (FEV1), and Forced Expiratory Flow 25–75 % (FEV 25–75 %), suggesting that prenatal PAH exposure inhibits the full development of respiratory airway caliber [147]. A study in northern Moravia region at Czech Republic, a known region with high concentrations of PAHs in Europe, showed an association between prenatal PAH exposure and intrauterine growth retardation (IUGR) and higher prevalence of asthma [148]. Certain PAHs resemble steroid hormones and are considered endocrine disruptors [149]. They are lipid soluble, and are transferred across the placenta and the fetal blood brain barrier [150]. These results collectively demonstrate that there are complex relationships between PAH exposure and asthma development, and multiple potential mechanisms might mediate this web of causation.

Future directions

The underlying cause of the association between air PM exposure and childhood asthma is unclear. A variety of constituents of PM are potential candidates for contributing to asthma initiation, exacerbation and progression. These include common allergens, microbial products, irritants, PAHs, carbon black, and sensitizing agents. Research is needed to clarify the associations between these constituents of PM and childhood asthma in order to focus efforts to develop effective prevention measures. This approach could lead to direct pollutant-control strategies toward those sources or constituents responsible for the greatest burden of risk for childhood asthma development and morbidity [151]. Further investigation of the interactions between multiple potential causative agents is needed to clarify potential mechanisms underlying these associations in order to enhance our ability to understand the pathogenesis of this disease and its treatment.

Conflict of interest None.

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