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Chronic Diseases and Translational Medicine 4 (2018) 75–94

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Perspective

Air pollutants and early origins of respiratory diseases

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Received 20 October 2017

Available online 7 June 2018

Abstract

Air pollution is a global health threat and causes millions of human deaths annually. The late onset of respiratory diseases in children and adults due to prenatal or perinatal exposure to air pollutants is emerging as a critical concern in human health. Pregnancy and fetal development stages are highly susceptible to environmental exposure and tend to develop a long-term impact in later life. In this review, we briefly glance at the direct impact of outdoor and indoor air pollutants on lung diseases and pregnancy disorders. We further focus on lung complications in later life with early exposure to air pollutants. Epidemiological evidence is provided to show the association of prenatal or perinatal exposure to air pollutants with various adverse birth outcomes, such as preterm birth, lower birth weight, and lung developmental defects, which further associate with respiratory diseases and reduced lung function in children and adults. Mechanistic evidence is also discussed to support that air pollutants impact various cellular and molecular targets at early life, which link to the pathogenesis and altered immune responses related to abnormal respiratory functions and lung diseases in later life.

Keywords: Air pollutants; Polycyclic aromatic hydrocarbon; Particulate matter; Early disease origin; Respiratory diseases

Air pollution has become a major global threat to human health. Historically, multiple major episodes of air pollution occurred world wide in the early twentieth century have produced severe health outcomes. Most tragically, the "killer fog" in London in 1952 has caused 12,000 unexplained deaths and severe long-term effects in human health.[1] Even in 2012, indoor and outdoor air pollution still caused an estimated 6.5 million deaths, which covers 11.6% of total global deaths.[2] Exposure to air pollutants mostly occurs in industrial and rural areas due to various manufacturing, traveling, and living activities. Multiple review articles and meta-analyses have described a direct impact of air pollutants on respiratory responses and diseases.[3–7] We will focus on the liaison of the later onset of respiratory diseases in childhood and adulthood with early life exposure to air pollutants at prenatal and perinatal stages.

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2018.03.003

Air pollutants

Air pollutants have complex chemical and physical features dependent on the sources of pollutants. Outdoor air pollutants are either derived from human activities, such as industrial emissions, road traffic, residential heating, shipping, air traffic, construction, agricultural activities, war and fire accidents, or from natural hazards, such as earthquake, tsunami, volcanic eruption, spontaneous forest fires, and extreme temperature.[8,9] Although natural hazards occur independent of human activities, they affect the living environment, health, and lives of humans as hazardous events.[4,10] Indoor air pollutants are generally released from smoking, building materials, air conditioning, house cleaning or air refreshing proucts, heating, lighting, and wood, fuel, or coal usage in cooking.[6] Chemically, these pollutants can be presented as the vapor forms of inorganic pollutants, such as ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), or as the vapor forms of organic pollutants, such as polycyclic aromatic hydrocarbons (PAHs), monocyclic hydrocarbons benzene, toluene, xylene, and aliphatic chemicals.[4,5] The particulate forms of air pollutants, however, usually consist of an inner carbon core with various organic pollutants and/or heavy metals on the surface (Fig. 1). The most harmful forms of particulate matter (PM) include PM_{10} (<10 μm in aerodynamic diameter), fine particles $PM_{2.5}$ (<2.5 μm), and ultrafine particles (less than 0.1 μm or 100 nm), which can be released from diesel engines, volcanoes, asbestos, unpaved roads, plowing, burning fields, lint, pollens, and spores.[11,12] Detailed chemical components of these air pollutants have been summarized in multiple reviews[4–6,13–15] and we will focus on the health impact of these air pollutants with different chemical and physical natures.

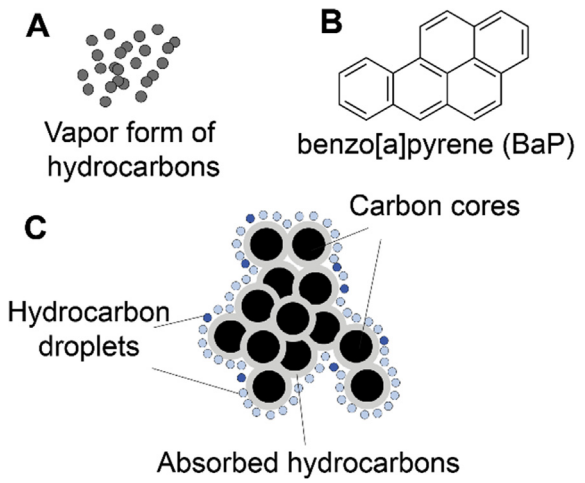

Fig. 1. Schematic demonstration of air pollutants: the vapor form (A) of organic air pollutants exemplified with the structure of benzo [a] pyrene (B) and the particulate form (diesel exhaust particles or particulate matters) of air pollutants (C).

Air pollution in respiratory diseases

Although the bronchopulmonary tract has multiple protective mechanisms, such as mucosal cilia and air-blood barrier, air pollutants are able to accumulate in or pass through lung tissues dependent on the size and chemical nature of pollutants.[13] The vapor of air pollutants is prone to be absorbed by human tissues or dissolved in body fluids, mainly relying on their hydrophilicity and hydrophobicity. PM_{10} particles with larger size (~10 μm) are able to reach the proximal airways and be mostly eliminated by mucociliary clearance. $PM_{2.5}$, as a notable risk factor for health, can invade more deeply into the lungs.[10,16,17] The ultrafine particles are capable of translocation through blood circulation to distal organs and tissues, such as liver tissue for detoxification and placental tissues during pregnancy.[10] Negative health effects of air pollutants have been shown on multiple respiratory diseases, including respiratory infections,[18–20] asthma,[21,22] chronic obstructive pulmonary disease (COPD),[23] lung cancer, even in combination with stroke and heart diseases as reviewed.[3,24–26] We briefly outline these direct negative effects of air pollutants on major respiratory diseases as below.

Respiratory infections

Air pollution enhances the severity of respiratory infections, particularly in children.[18–20] Especially, outdoor pollution in large cities is associated with a high burden of various acute respiratory infections, which together are responsible for nearly a third of all deaths in children under 5 years old.[18] Exposure to NO_2 and PMs in five German cities was associated with increasing cases of laryngo-tracheo-bronchitis mostly due to influenza viral infections.[27] Another study conducted in three cities in Finland supported similar conclusions.[28] However, indoor pollution contributes to high rates of chronic bronchitis of non-smoker cooking mothers in hilly regions of Nepal,[29] suggesting that indoor pollution is likely more associated with respiratory infections in developing countries and rural areas. The adverse impact of air pollutants can be highlighted especially in individuals with pre-existing lung infections or other lung diseases, because they are likely at greater risk, and also in children, possibly

because children have a relatively larger lung surface area and more outdoor physical activities with a greater chance to expose to air pollution.[30]

Asthma and COPD

Emergency visits for asthma are mostly related to the exacerbation effect of environmental exposure. Both major outdoor and indoor pollutants, including O_3, CO, NO_2, SO_2, PM_{10}, $PM_{2.5}$, dust mite, pollen, pet dander, and smoke, contribute to more severe allergic responses. Specifically, allergic immunoglobulin E (IgE) responses to pollen or ovalbumin can be triggered by diesel exhaust particles (DEP) exposure[31,32] and airway responsiveness in asthmatic patients with house dust mite challenge can be potentiated by short-term exposure to nitrogen oxides.[33] Similarly, long-term exposure to indoor air pollution from second-hand cigarette smoke and biomass fuel is able to induce chronic inflammation that contributes to COPD,[23] while exposure to PMs is linked to the acute exacerbation-related hospitalization of COPD patients.[34] Overall, more epidemiological associations have been reported to link the exposure to air pollutants with the development of asthmatic and chronic inflammation.[3,7,24,25,35]

Lung cancers

Although cigarette smoking is considered as a leading contributor to cancer-related death worldwide,[36] multiple additional risk factors, including both indoor[37] and outdoor[38] air pollution, also contribute to the development of lung cancers. The air pollution exposure-induced pathogenesis of lung cancer is closely related to DNA injury, DNA adduct formation, chromosomal aberrations, and methylation modifications, some of which are under development as biomarkers of lung cancers relative to ambient air pollution exposure.[39] It was established at least with intensive epidemiological evidence that various air pollutants are directly associated with the high incident rate of lung cancers.[36–39] In this review, we will emphasize the epidemiological and toxicological evidence for the delayed onset of respiratory diseases with prenatal or perinatal exposure to air pollutants.

Air pollution in pregnancy disorders

Exposure to ambient air pollution during the pregnancy is considered having a long-term impact on human health. The prenatal stage is characterized with an exquisite inflammatory homeostasis in mother and mysterious organogenesis in developing fetus, together presenting a highly susceptible window in human lives for adverse effects of environmental pollutants.[40] Maternal exposure to air pollution can directly influence the fetus through the transfer of pollutant chemicals through amniotic fluid and placenta.[41,42] Evidence has been accumulated over past two decades to support the association of air pollutants with various adverse birth outcomes, including preterm birth (<37 weeks of gestational age), low birthweight (LBW) (<2500 g), small for gestational age (SGA), and intrauterine growth restriction (IUGR) (Table 1).[43]

Assessing air pollution has involved in environmental monitoring at specific areas of interest, at a national or global scale.[44,45] As a result, U.S. Environmental Protection Agency (EPA) established an Air Quality System (AQS) database, which provides hourly or daily concentrations of pollutants measured from 1980 through 2009 for different geographic areas. Researchers can utilize this database to make a daily, monthly, or year-long estimation of air pollution exposure in a residence of study.[46,47] Alternatively, exposure to traffic-related air pollution has been simply estimated using distance, such as for the residence within 50 meters from highways, and further used to determine the association with the risk of adverse birth outcomes in Vancouver, Canada.[48] However, we will focus on the common methods for monitoring individual exposure and pollutant metabolites, which are important to be considered in the pathogenesis of diseases. Personal air monitoring is one of the commonly used methods to measure individual exposure. The subjects are required to carry a personal monitor to collect vapors and particles of airborne pollutants on a microfiber filter.[49] The individual exposure level during a monitoring period can be estimated by the calculation of accumulated pollutants, such as $PM_{2.5}$, using device-specific parameters. The devices and methods to monitor personal exposure has also been comprehensively reviewed elsewhere.[50] Urinary metabolites provide a convenient biological source to monitor both the amount of intake pollutants and the metabolites of individual pollutant chemicals. For example, the urinary pyrene metabolite 1-hydroxypyrene has been broadly used to reflect the individual exposure level to PAHs.[51] Measuring urinary metabolites of pollutants further provide a sustainable approach to assess individual exposure at a long term process; thus, it is highly feasible in pre- and peri-natal exposure estimation.[52] Thirdly, the pollutant levels in blood and tissues are also measured to show

Table 1
Adverse pregnancy disorders and birth outcomes with prenatal exposure to air pollution.

Air pollutants	Outcomes	Cohorts/analysis	Major findings	Reference
Traffic-related air pollutants	LBW SGA	Vancouver, British Columbia, Canada	Decreased birth weight and short for gestational age LBW: 11%; 95%*CI* = 1.01 to 1.23 SGA: 26%; 95%*CI* = 1.07 to 1.49	Brauer et al[48,55]
CO	LBW Preterm birth	Meta-analysis[a]	Decreased birth weight and increased risk of preterm birth LBW: 11.4 g; 95% *CI* = (−6.9 to 29.7) g Preterm birth: *OR* = 1.04; 95%*CI* = 1.02 to 1.06	Stieb et al[56]
	LBW	Northeastern cities in U.S.: Boston, Hartford, Philadelphia, Pittsburgh, Springfield, and Washington, DC	Decreased birth weight *AOR* = 1.31; 95% *CI* = 1.06 to 1.62	Maisonet et al[59]
	LBW	Seoul, South Korea	Decreased birth weight *AOR* = 1.08; 95% *CI* = 1.04 to 1.12	Ha et al[60]
	IUGR	Calgary, Edmonton, and Montreal, Canada	Increased risk of intrauterine growth restriction First trimester: *OR* = 1.18; 95% *CI* = 1.14 to 1.23 Second trimester: *OR* = 1.15; 95% *CI* = 1.10 to 1.19 Third trimester: *OR* = 1.19; 95% *CI* = 1.14 to 1.24	Liu et al[61]
	Cardiac ventricular septal defects	California Birth Defects Monitoring Program	Increased risk of cardiac ventricular septal defects 2nd quartile: *OR* = 1.62; 95% *CI* = 1.05 to 2.48 3rd quartile:*OR* = 2.09; 95% *CI* = 1.19 to 3.67 4th quartile:*OR* = 2.95; 95% *CI* = 1.44 to 6.05	Ritz et al[62]
NO_2	LBW	Meta-analysis[a]	Decreased birth weight: 28.1 g; 95% *CI* = (11.5 to 44.8) g	Stieb et al[56]
	LBW	Connecticut and Massachusetts	Decreased birth weight: 8.9 g; 95% *CI* = (7.0 to 10.8) g	Bell et al[58]
	LBW Reduced birth length Smaller HC SGA	INMA cohort in Valencia	Various birth outcomes including LBW: −40.3 g; 95% *CI* = (−96.3 to 15.6) g Birth length: −0.27 cm; 95% *CI* = (−0.51 to −0.03) cm HC: −0.17 cm; 95% *CI* = (−0.34 to −0.003) cm SGA: *OR* = 1.37; 95% *CI* = 1.01 to 1.85	Ballester et al[63]
	LBW	Seoul, South Korea	Decreased birth weight *AOR* = 1.07; 95% *CI* = 1.03 to 1.11	Ha et al[60]
	LBW Smaller HC	Netherlands	Decreased birth weight and head circumference LBW: −3.4 g; 95% *CI* = (−6.2 to −0.6) g HC: −0.12 mm; 95% *CI* = (−0.17 to −0.06) mm	van den Hooven et al[47]
	LBW	European cohort study (ESCAPE)	Decreased birth weight *OR* = 1.06; 95% *CI* = 1.01 to 1.11	Pedersen et al[64]
	IUGR	Calgary, Edmonton, and Montreal, Canada	Increased risk of intrauterine growth restriction First trimester: *OR* = 1.16; 95% *CI* = 1.09 to 1.24 Second trimester: *OR* = 1.14; 95% *CI* = 1.06 to 1.21 Third trimester: *OR* = 1.16; 95% *CI* = 1.09 to 1.24	Liu et al[61]
SO_2	LBW	North eastern cities in US: Boston, Hartford, Philadelphia, Pittsburgh, Springfield, and Washington, DC	Decreased birth weight 25 to < 50th percentiles: *AOR* = 1.21; *CI* = 1.07 to 1.37 50 to < 75th percentiles: *AOR* = 1.20; *CI* = 1.08 to 1.35 75 to < 95th percentiles: *AOR* = 1.21; *CI* = 1.03 to 1.43	Maisonet et al[59]
	LBW	Beijing, China	Decreased birth weight: 7.3 g; *OR* = 1.11; 95% *CI* = 1.06 to 1.16	Wang et al[65]
	LBW	Seoul, South Korea	Decreased birth weight *AOR* = 1.06; 95% *CI* = 1.02 to 1.10	Ha et al[60]
PM_{25}	LBW	Meta-analysis[a]	Decreased birth weight *OR* = 1.05; 95% *CI* = 0.99 to 1.12	Stieb et al[56]
	LBW	Connecticut and Massachusetts	Decreased birth weight: 14.7 g; 95% *CI* = (12.3 to 17.1) g	Bell et al[58]
	LBW	European cohort study (ESCAPE)	Decreased birth weight *OR* = 1.18; 95% *CI* = 1.06 to 1.33	Pedersen et al[64]

(*continued on next page*)

Table 1 (*continued*)

Air pollutants	Outcomes	Cohorts/analysis	Major findings	Reference
	LBW	International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO)	Decreased birth weight *OR* = 1.10; 95% *CI* = 1.03 to 1.18	Dadvand et al[66]
	IUGR	Calgary, Edmonton, and Montreal, Canada	Increased risk of intrauterine growth restriction First trimester: *OR* = 1.07; 95% *CI* = 1.03 to 1.10 Second trimester: *OR* = 1.06; 95% *CI* = 1.03 to 1.10 Third trimester: *OR* = 1.06; 95% *CI* = 1.03 to 1.10	Liu et al[61]
PM_{10}	LBW Preterm birth	Meta-analysis[a]	Decreased birth weight and increased risk of preterm birth LBW: *OR* = 1.10; 95% *CI* = 1.05 to 1.15 Preterm birth: *OR* = 1.06; 95% *CI* = 1.03 to 1.11	Stieb et al[56]
	LBW Preterm birth	Los Angeles, California	Decreased birth weight and Increased risk of preterm birth LBW: *OR* = 1.21; 95% *CI* = 0.85 to 1.74 Preterm birth: *OR* = 1.17; 95% *CI* = 0.92 to 1.50	Wilhelm et al[57]
	LBW Preterm birth Smaller HC SGA	Netherlands	Various birth outcomes including, LBW: −3.6 g; 95% *CI* = (−6.7 to −0.4) g Preterm birth (3rd quartile): *OR* = 1.40; 95% *CI* = 1.03 to 1.89 Preterm birth (4th quartile): *OR* = 1.32; 95% *CI* = 0.96 to 1.79 HC: −0.18 mm; 95% *CI* = (−0.24 to −0.12) mm SGA: *OR* = 1.38; 95% *CI* = 1.00 to 1.90	van den Hooven et al[47]
	LBW	European cohort study (ESCAPE)	Decreased birth weight *OR* = 1.16; 95% *CI* = 1.00 to 1.35	Pedersen et al[64]
	LBW	International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO)	Decreased birth weight *OR* = 1.03; 95% *CI* = 1.01 to 1.05	Dadvand et al[66]
	LBW	Connecticut and Massachusetts	Decreased birth weight: 8.2 g; 95% *CI* = (5.3 to 11.1) g	Bell et al[58]
Polycyclic aromatic hydrocarbons (PAHs)	LBW Smaller HC	Dominican and African-American residing in Washington Heights, Central Harlem, and the South Bronx, New York	Decreased birth weight and smaller head circumference LBW: *P* = 0.003 HC: *P* = 0.01	Perera et al[67]
	Preterm birth Increased IUGR SGA	New York City, U.S.	Various birth outcomes including SGA: *OR* = 1.9; 95% *CI* = 1.1 to 3.5 IUGR: 4% decrease; *P* = 0.241 Preterm birth: 5-fold increase; 95% *CI* = 1.8 to 11.9; *P* = 0.001	Choi et al[68]
Total suspended particles (TSP)	LBW	Beijing, China	Decreased birth weight: 6.9 g; *OR* = 1.10; 95% *CI* = 1.05 to 1.14	Wang et al[65]
	LBW	Seoul, South Korea	Decreased birth weight *AOR* = 1.04; 95% *CI* = 1.00 to 1.08	Ha et al[60]

LBW: low birth weight; *CI:* confidence intervals; SGA: small for gestational age; *OR:* odds ratios; *AOR:* adjusted odds ratio; IUGR: intrauterine growth restriction; HC: head circumference.

[a] Meta-analysis with EMBASE, MEDLINE, Scopus, Current Contents, Global Health, Cochrane, TOXLINE and the Canadian Research Index.

the specific level of pollutants or their metabolites that interact with cells and tissues, such as PAH-DNA adducts, including benzo[a]pyrene diol-epoxide DNA adducts, from blood and placenta tissues.[53,54] As the individual exposure levels are measured, the biological outcomes of exposure to specific pollutant chemicals can be further investigated and concluded.

Low birthweight and restrictions in fetal growth

LBW is a common indicator of adverse birth outcomes in the studies related to environmental exposure (Table 1) in meta-analyses based upon previously reported epidemiological studies, the decrease of birth weight (e.g., 10−30 g; 95% *CI* = −69 to 297)

and increased odds ratio (*OR*) of LBW (e.g., *OR* = 105−110) are strongly associated with the exposure to outdoor CO, NO_2, PM_{10}, and $PM_{2.5}$.[56] In these studies, confident interval (*CI*) was used to show a range within which 95% of values lies and *OR* was calculated as a probability ratio of presented property to absent property. The impact of air pollution on LBW has become a critical global health concern. The researchers in Spain found that NO_2 exposure during the pregnancy was associated with a reduction in birth weight (−40.3 g) and birth length (−0.27 cm) along with a smaller head circumference (−0.17 cm), showing a linear relationship to the risk of SGA.[63] Other studies for exposure to PAHs in New York,[67] and exposure to NO_2, SO_2, CO, PM_{10}, and PM_{25} in Los Angeles,[57] Connecticut, Massachusetts,[58] and other northeastern cities[59] have similarly supported an increase of the risk for LBW and preterm. In Beijing of China and Seoul of South Korea with high air pollution in Asia, researchers reported the increased risk of LBW associated with CO, total suspended particles, and SO_2.[60,65] Additionally, European (ESCAPE) and international (ICAPPO) cohort studies combining multiple populations in different countries reported the effect of maternal exposure to air pollutants, including PM_{10} and $PM_{2.5}$, on increased risk of LBW at term.[64,66] Trimester effects of air pollution exposure during pregnancy have been indicated in some studies (Table 1). Van den Hooven et al[47] found that prenatal exposure to both PM_{10} and NO_2 in the third trimester were inversely associated with birth weight (−3.6 g and −3.4 g) and fetal head circumference (−0.18 mm and −0.06 mm), and increased risk of SGA particularly with PM_{10}. Some epidemiological studies also suggested certain unknown biological factors in different ethnical populations may influence the risk of environmental exposure in LBW. The association of PAH exposure with significantly reduced birth weight was observed in the Krakow Caucasians in Poland, while a 6-fold greater risk of LBW with PAH exposure was observed in New York City (NYC) African Americans than the risk in Krakow Caucasians. However, this association is missing in NYC Dominicans.[68,69] These results likely reflect that the impact of air pollution can be more susceptible to a certain ethnic group such as African Americans, suggesting the importance of gene and environmental interactions in the development of LBW. Additionally, numbers of researchers have investigated whether these abnormal birth outcomes can be reversed when air pollution is reduced, and interestingly, they were able to find that the risk of LBW could be prevented when air pollution was declined.[64,70]

Preterm

Around 10% of all births are preterm with a gestation period less than 37 weeks in the United States[71] and approximately 11% of births worldwide are preterm.[72] Preterm birth, including 3% of very early preterm cases with gestation period less than 27 weeks, is connected to the maternal exposure to various environmental pollutants including smoking and air pollution containing PAHs[73−77](Table 1). Both vapor and particulate pollutants, including CO, NO_2, PM_{10}, and $PM_{2.5}$, had an adverse effect on preterm birth, for example, PM_{10} exposure in a Netherlands cohort study associated with the increased risk of preterm birth.[47] However, results were less consistent for O_3 and SO_2, suggesting that there are variabilities of outcomes among each component of environmental chemicals.[56] Risk of air pollution exposure to preterm birth may also be different in various human populations. Similar to LBW among African-American population, 5-fold greater risk of preterm birth also attributed to environmental tobacco smoke (ETS) in addition to the effect of prenatal PAH exposure on an increased risk of growth restriction.[51] Moreover, preterm birth has been shown to have a general long-term effect on the lung function,[78] which will be further discussed for its impact on later onset of respiratory diseases.

Deficit in respiratory system

While many studies have focused on the inadequate fetal growth and development, some studies have specifically related the birth defects of multiple organ systems with the exposure to the air pollution. Cigarette smoke impacts the development of multiple systems, including the respiratory, nervous, and cardiac systems, during pregnancy.[79] For the respiratory system, the effect of air pollution on prenatal and perinatal lung disorders was mostly learned from the pregnancy with smokers or second-handed smokers. Pollutants derived from cigarette smoke are able to cross the placental barrier and causing multiple adverse effects on the fetal development, including chronic hypoxia, lung function, lung morphology such as branching and alveolarization.[80] In animal models, such as rhesus monkeys, prenatal nicotine exposure alters pulmonary function in newborns.[81] Both pulmonary functional and anatomic changes associated with maternal smoking and nicotine, which has most detrimental effects on the early development of the lung, are suggested to induce later respiratory illness[79−81] and will be detailed below.

Epidemiological evidence for early origins of respiratory diseases

The Great Smog of London in 1952[82] built up a relationship between perinatal exposure to air pollution and the later development of respiratory diseases in life. A recent study analyzed the prevalence of asthma in the population exposed to the Great Smog *in utero* or in the first year of life. The results showed that exposure has increased the probability of asthma in both childhood (19.87%) and adulthood (9.53%)[83] (Table 2), supporting that the early life and prenatal exposure to air pollution conveys a long-term effect in children and adults. Several other studies have similarly provided evidence supporting this interesting connection of early exposure to air pollutants and its long-term effect,[84–87] including studies in China that supported incidence of asthma, allergic rhinitis, and eczema in children was associated with maternal exposure to traffic-related pollutants during entire pregnancy.[87] Multiple human cohort studies on tobacco smoking during the pregnancy period show the impact on placental function, fetal lung development, and further impact on the respiratory function of newborns and children. Symptomatically, maternal smoking will lead to an increased risk of pulmonary viral and bacterial infections, wheezing, reduced respiratory function reflected by low forced expiratory volume in 1 second (FEV1), asthma, and COPD.[88–90]

Abnormal respiratory function

Abnormal respiratory function in late life is now known able to be induced by early exposure to air pollution[120] and provoke long-term respiratory diseases.[121] The early exposure in human life can first reduce the pulmonary function, which is usually measured by FEV1 and forced vital capacity (FVC), as summarized (Table 2). Several studies are detailed here. For example, reduced lung function with low FEV1 in children at preschool age was associated with exposure to high level of benzene and NO_2 during pregnancy in a study from Spain.[111] The FVC and FEV1 of asthmatic children with asthma diagnosis before age 2 and maternal smoking were negatively affected by the exposure to CO, PM_{10}, and NO_2 during the second-trimester of pregnancy in a California study.[122] Another birth cohort study from Switzerland showed that prenatal exposure to PM_{10} was associated with higher minute ventilation and respiratory need in newborns.[116] In addition to inorganic pollutants, perinatal exposure to ambient organic pollutants PAHs increases the risk of various respiratory symptoms during early infancy, including barking cough, wheezing, sore throat, ear infection, and cough irrespective of respiratory infections, independent of passive tobacco smoking.[118]

The impact of maternal smoking and related pregnancy complications on the lung function of offspring spans from infants[96] to children,[123] and to adolescents.[124,125] Maternal exposure to smoke as an example with mixed pollutants has been consistently associated with the reduction of FEV1 and maximal expiratory flow in children and young adults,[98] together with a similar effect from E-cigarettes smoking.[80] As a consequence, maternal smoking increases the susceptibility of fetus and newborns to illnesses with a greater deficit in lung function than those whose parents did not smoke,[104] especially with respiratory diseases in children as reflected by an impaired lung function. In reported multiple birth cohort studies (Table 2), maternal smoking in pregnancy independently resulted in a 39–65% increased risk of wheezing and asthma at 4–6 years of age.[126] A similar result with a 28–52% increased risk of wheezing in children was also shown from a meta-analysis of 79 cohorts.[91] Additionally, a retrospective study with 20,000 children at the age of 6–12 years reported that maternal smoking is independently associated with a reduced lung function indicated by a lower FEV1.[102] The outcomes induced by the effect of maternal smoking can be added up together with the other factors, such as viral infection, airway inflammation, and even epithelial metastasis. For example, the smokers with lower respiratory illnesses, caused by a viral infection from their early life, are more likely to develop asthma in adult.[127]

Respiratory infections

Because of the high prevalence of childhood respiratory infections in areas with severe air pollution,[18–20] an epidemiological study on the association of later respiratory infections with maternal exposure to air pollutants is particularly meaningful. As summarized in Table 2, it was reported from a Spanish cohort that infants during the 12–18 months of age showed a relationship between the increased risk of respiratory illness, such as lower respiratory tract infection (LRTI) in this study, and exposure to NO_2 ($RR = 1.05$) and benzene ($RR = 1.06$).[112] More recent meta-analysis of 10 European birth cohorts (ESCAPE) study found a significant association between air pollution, measured with PM_{10}, and NO_2 levels, and pneumonia.[113] Although it was well established that microbes are critical in the pathogenesis of respiratory diseases, air

Table 2
Prenatal exposure to air pollutants contributes to the onset of respiratory disorders in childhood and adulthood.

Air pollutants	Respiratory disorders	Onset stage	Cohorts/analysis	Major findings	Reference
Maternal exposure to second-hand smoke (SHS); environmental tobacco smoke (ETS)	Asthma Wheeze	Children Adolescents	Meta-analysis with 79 cohorts	Increased risk of asthma and wheezing (>20%) wheeze: *OR* = 1.70; 95% *CI* = 1.24 to 2.35 asthma: *OR* = 1.85; 95% *CI* = 1.35 to 2.53	Burke et al[91]
	Asthma Wheeze	Children	Meta-analysis with 43 papers	Increased risk of asthma and wheezing *OR* = 1.21; 95% *CI* = 1.13 to 1.31	Silvestri et al[92]
	Respiratory symptoms Lower airway obstruction	Children	United States (St. Louis, Missouri, US, and Cleveland, Ohio) and London, England	Increased respiratory symptoms and risk of lower airway obstruction FEV1/FVC: 18.9%; $P < 0.001$ Mid-expiratory phase/FVC ratio: 0.15; $P = 0.001$ Bronchodilator responsiveness: 12%; $P = 0.03$	Cohen et al[93]
	Reduced pulmonary function COPD	Adults	European Community Respiratory Health Survey	Reduced FEV1 and increased risk of COPD FEV1 (men): 95 mL; 95% *CI* = (67 to 124) mL FEV1 (women): 60 mL; 95% *CI* = (40 to 80) mL Increased COPD (men): 1 factor; *OR* = 1.7; 95% *CI* = 1.1 to 2.6 Increased COPD (women): >3 factors; *OR* = 1.6; 95% *CI* = 1.01 to 2.6	Svanes et al[94,95]
Maternal exposure to smoke	Peripheral airflow obstruction	Infants	105 infants from Louisville, KY	Altered lung function, and a response to a bronchodilator [FEF25]/PFEF = 0.119 ± 0.036 ($P < 0.0005$)	Sheikh et al[96]
	Asthma	Children	58,841 children born in Finland in 1987	Increased risk of asthma: 25-36%; *OR* = 1.25; 95% *CI* = 1.09 to 1.44	Jaakkola et al[97]
	Reduced pulmonary function	Children Adults	Meta-analysis with 692 articles from the Embase and Medline databases	Reduced FEV1 Mid-expiratory flow rates: 5.0% reduction; 95% *CI* = 3.3% to 6.6% End-expiratory flow rates: 4.3% reduction; 95% *CI* = 3.1% to 5.5%	Cook et al[98]
	Respiratory symptoms	Children	Kingston allergy birth cohort (KABC)	Decreased the rate of children without respiratory symptoms *HR* = 2.68; 95% *CI* = 1.48 to 4.84	North et al[99]
	Asthma Reduced pulmonary function	Children	12 southern California communities	Reduced FEV1 and FEF25−75 FEV1 (boys): −13.6%; 95% *CI* = −18.9% to −8.2% FEV25-75 (boys): −29.7%; 95% *CI* = −37.8% to −20.5% FEV25-75 (girls): −26.6%; 95% *CI* = −36.4% to −15.1%	Gilliland et al[100]
	Asthma	Children	Childhood Asthma Management Program	Reduced FEV1 and increased risk of asthma in GSTM1-null children FEV1/FVC = 83.8%; $P = 0.01$	Rogers et al[101]
	Reduced pulmonary function	Children	Meta-analysis with >20,000 children (aged 6−12 yrs.) from nine countries in Europe and North America	Reduced FEV1: 40%; 95% *CI* = 0.95% to 1.0%	Moshammer et al[102]

	Reduced pulmonary function	Adults	Mater−University of Queensland Study of Pregnancy (MUSP)	Reduced FEV1 and FEF25−75 Regression coefficient = −0.16; 95% *CI* = −0.30 to −0.02	Hayatbakhsh et al[103]
	Reduced pulmonary function	Adults	Tucson Children's Respiratory Study	Reduced FEV1/FVC 2.8%; 95% *CI* = 0.9%−4.8%; *P* = 0.003	Guerra et al[104]
	Asthma Wheeze	Adolescents	Western Australian Pregnancy (Raine) Cohort	Increased risk of asthma and wheezing wheeze: *OR* = 1.77, 95% *CI* = 1.14−2.75 asthma: *OR* = 1.84, 95% *CI* = 1.16−2.92	Hollams et al[105]
	Asthma	Adults	German Multicenter Allergy Study (MAS-90)	Increased risk of asthma *HR* = 1.79; 95% *CI* = 1.20 to 2.67	Grabenhenrich et al[106]
	Asthma Wheeze	Children	Meta-analysis with 43 papers	Increased risk of asthma and wheezing Asthma: *OR* = 1.22; 95% *CI* = 1.03 to 1.44 Wheezing: *OR* = 1.36; 95% *CI* = 1.19 to 1.55	Silvestri et al[92]
	Asthma BHR	Adolescents Adults	Göteborg, Sweden	Increased risk of asthma *OR* = 3.5; 95% *CI* = 1.1 to 11.3	Goksör et al[107]
Industrial-related air pollutants	Asthma	Children Adults	Great smog exposed population in London	Increased risk of asthma Children: 19.87%; 95% *CI* = 3.37% to 36.38% Adult: 9.53%; 95% *CI* = −4.85% to 23.91%	Bharadwaj et al[83]
Traffic-related air pollutants	Asthma Wheeze Increased IgE	Children	Columbia Center for Children's Environmental Health birth cohort	Positive associations between air pollution and asthma, wheeze, and IgE Asthma: *OR* = 1.43; 95% *CI* = 1.03 to 1.97 Wheeze: *OR* = 1.26; 95% *CI* = 1.01 to 1.57 Increased IgE: *OR* = 1.25; 95% *CI* = 1.09 to 1.42	Patel et al[108]
	Asthma Dyspnea Wheeze	Children	Windsor Children's Respiratory Health Study	Increased risk of asthma, dyspnea, and wheeze Wheeze: *OR* = 1.23; 95% *CI* = 1.07 to 1.41 Dyspnea: *OR* = 1.27; 95% *CI* = 1.05 to 1.52 Asthma: 8%; *OR* = 1.08; 95% *CI* = 1.012 to 1.149	Dales et al[109]
	Asthma	Infants	Southwestern British Columbia (BC)	Increased risk of asthma: 12%; *OR* = 1.08; 95% *CI* = 1.04 to 1.12	Clark et al[110]
NO_2	Reduced pulmonary function	Children	Environment and childhood (INMA) project	Reduced FEV1: −28.0 mL; 95% *CI* = (−52.9 to −3.2) mL	Morales et al[111]
	LRTI	Infants	Environment and childhood (INMA) project	Increased risk of respiratory illness including LRTI *RR* = 1.05; 95% *CI* = 0.98 to 1.12	Aguilera et al[112]
	Pneumonia	Children	European cohort study (ESCAPE)	Increased risk of pneumonia *OR* = 1.30; 95% *CI* = 1.02 to 1.65	MacIntyre et al[113]
	Asthma Rhinitis Eczema	Children	2598 preschool children aged 3−6 years in China	Increased risk of asthma, rhinitis, and eczema Asthma: 6.8%; *OR* = 1.69; 95% *CI* = 0.99 to 2.70 Allergic rhinitis: 7.3%; *OR* = 1.63; 95% *CI* = 1.03 to 2.77 Eczema: 28.6%; *OR* = 1.37; 95% *CI* = 1.04 to 1.80	Deng et al[87]
$PM_{2.5}$	Asthma	Children	272 high-risk infants from Vancouver	Increased risk of asthma: 50%; *OR* = 3.1; 95% *CI* = 1.3 to 7.4	Carlsten et al[114]
PM_{10}	Reduced pulmonary function	Children	BAMSE (Children, Allergy,Milieu, Stockholm, Epidemiological Survey)	Reduced FEV1: −59.3 mL; 95% *CI* = (−113 to −5.6) mL	Schultz et al[115]
	Pneumonia	Children	European cohort study (ESCAPE)	Increased risk of pneumonia *OR* = 1.76; 95% *CI* = 1.00 to 3.09	MacIntyre et al[113]

(*continued on next page*)

Table 2 (*continued*)

Air pollutants	Respiratory disorders	Onset stage	Cohorts/analysis	Major findings	Reference
	Reduced pulmonary function	Infants	Bern, Switzerland	Increase in minute ventilation 24.9 mL/min; 95% *CI* = (9.3 to 40.5) mL/min	Latzin et al[116]
Benzene	Reduced pulmonary function	Children	Environment and childhood (INMA) project	Reduced FEV1: −18.4 mL; 95% *CI* = (−34.8 to −2.1) mL	Morales et al[111]
	LRTI	Infants	Environment and childhood (INMA) project	Increased risk of respiratory illness including LRTI *RR* = 1.06; 95% *CI* = 0.94 to 1.19	Aguilera et al[112]
Diesel exhaust particles (DEPs)	Wheeze	Infants	The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS)	Increased risk of wheezing *OR* = 2.50; 95% *CI* = 1.15 to 5.42	Ryan et al[117]
Polycyclic aromatic hydrocarbons (PAHs)	Respiratory symptoms	Infants	333 newborns in Krakow, Poland	Increased respiratory symptoms Barking cough: *RR* = 4.80; 95% *CI* = 2.73 to 8.44 Wheezing without cold: *RR* = 383; 95% *CI* = 1.18 to 12.43 Sore throat: *RR* = 1.96; 95% *CI* = 1.38 to 2.78 Ear infection: *RR* = 1.82; 95% *CI* = 1.03 to 3.23 Cough irrespective of respiratory infections: *RR* = 1.27; 95% *CI* = 1.07 to 1.52 Cough without cold: *RR* = 1.72; 95% *CI* = 1.02 to 2.92	Jedrychowski et al[118]
	Asthma	Children	Columbia Center for Children's Environmental Health birth cohort	Increased risk of allergic sensitization *RR* = 1.15; *P* = 0.001	Perzanowski et al[119]

OR: odds ratios; *CI:* confidence intervals; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; FEF: forced expiratory flow; PEF: peak expiratory flow; *HR*: hazard ratio; FEV25-75: forced expiratory volume at 25%−75%; BHR: bronchial hyper-responsiveness; IgE: immunoglobulin E; LRTI: lower respiratory tract infection.

pollutants are able to interplay with both host and microbial factors and alter the disease course.

Allergy

Allergic respiratory diseases are induced by multiple genetic and environmental factors interlinked through IgE- and non-IgE-associated mechanisms.[128] Allergens are necessary factors to stimulate allergic diseases, while air pollutants usually worsen allergic responses. Perinatal exposure to PAHs enhances the allergic responses to cockroach allergen as in a study with New York urban population.[119] As distance to heavily trafficked intersections was used to indicate an exposure level to motor vehicle exhaustion and traffic-derived pollutants, children living closer to these intersections can be found with increased IgE levels.[108] Exposure to diesel exhaust particles was associated with persistent wheeze by 36 months of age[117] and enhanced allergic responses to allergens in human population.[129,130] In addition to vapor and particulate forms of PAHs, asthma in later life stages was also associated with maternal smoking.[100,131] Maternal tobacco smoking during the pregnancy increases the risk of developing asthma in children at the age of 7 years according to a study from Boston and Finnish cohorts.[97] A similar effect was also observed in an exposure to second-hand tobacco smoke for the occurrence of asthma and wheeze symptoms[132] or the onset of asthma and more severe airflow obstruction in the younger age of children.[101] Overall, the association of later onset of asthma with maternal exposure to air pollutants is well supported by epidemiological evidence.

COPD

COPD has been considered as a disease that occurs mostly in aging groups, while increasing evidence recently supported that COPD may originate from environmental exposure in the maternal stage as recently reviewed.[84,95,133] We have discussed that maternal exposure to air pollutants is associated with lower lung function in infancy, which can be further associated with adult lung function and COPD.[94,95] More evidence also shows postnatal or childhood exposure to air pollutants has vast impact on later development of COPD. For indoor exposure, around 35% of individuals with COPD in developing areas associated with the exposure to indoor smoke and biomass fuel combustion.[134] In these cases, the biomass fuels, such as coal, straw, crop residues, wood, and animal dung, were used to heat and cook in the poorly ventilated household. For outdoor pollutants, the PM, O_3, and SO_2 from vehicle traffic and fuel combustion are also associated with respiratory disorders.[135] Children living within 500 meters of a major freeway in southern California showed a deficit of FEV1 when compared with children who lived at least 1500 meters away from a freeway, as it is associated with COPD.[135] For the particulate forms of chemical pollutants, increased PM_{10} exposure is associated with reduced lung function in children. While moved to areas with lower PM_{10} levels, these children showed an improved lung function.[136] In the UK, higher carbon content in airway macrophages in induced sputum samples from the school children was associated with PM_{10} levels, which was further significantly correlated with lower respiratory function.[137] The epidemiological evidence supporting the association of exposure to various air pollutants in childhood or adolescence with abnormal developmental outcomes of lung and later COPD diseases will facilitate the elucidation of molecular and cellular mechanisms contributing to the long-term adverse effects of air pollutants on COPD and other respiratory diseases.

Mechanistic evidence for prenatal disease origins

Although intensive epidemiological studies support the association of air pollution with abnormal birth outcomes, a high degree of variabilities among epidemiological studies requires more stringent control groups with less divergence in confounding factors.[138] Findings in toxicological studies[56] have started shedding some light on the prenatal origin of later respiratory diseases. Hypothetical mechanisms consider the impact of air pollutants on various myeloid, lymphoid, and stromal cells to produce: (1) transcription factors to control gene expression; (2) growth factors to control lung tissue development at early stages; (3) cytokines and chemokines to regulate tissue inflammatory responses (Fig. 2).

Oxidation responses

Maternal smoking is one of the well-studied environmental factors altering lung function. Nicotine is able to cross placenta and exists in amniotic fluid, allowing nicotine to interact with the receptor expressed in the fetal airway and alter the development of fetal lung tissues.[139] Meanwhile, nicotine was shown to increase the production of reactive oxygen species (ROS) and reduce the production of antioxidants, leading to an unbalanced oxidant-antioxidant environment and an adverse effect on cell integrity.[140] This

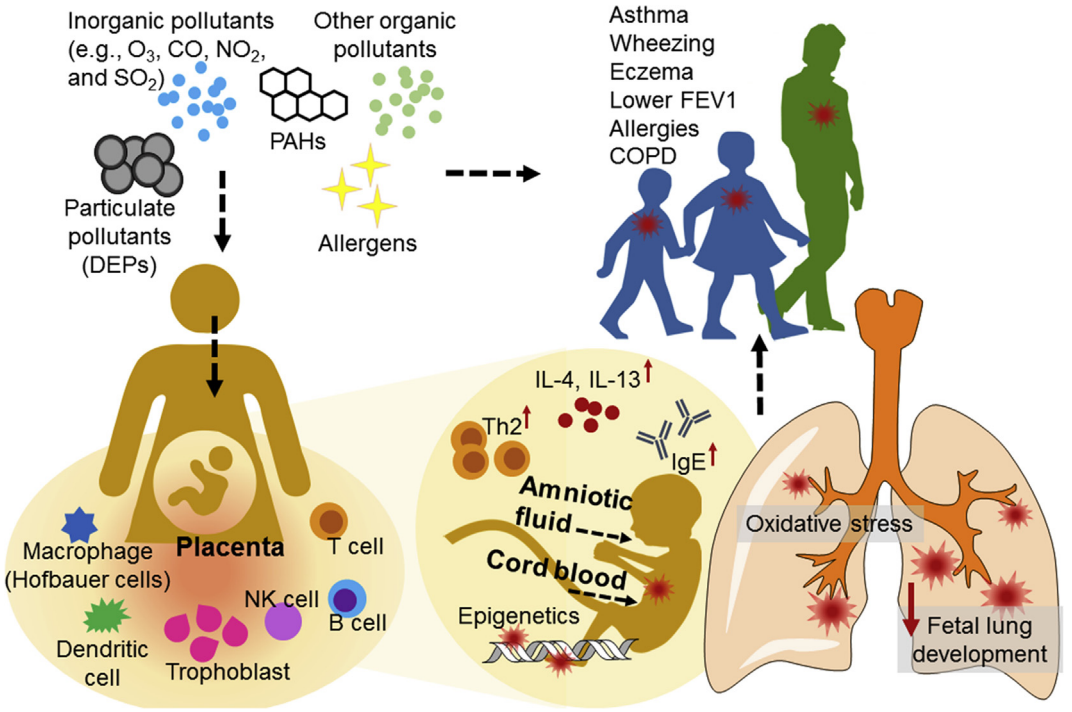

Fig. 2. Schematic demonstration of prenatal origin of respiratory diseases. PAH: polycyclic aromatic hydrocarbon; FEV1: forced expiratory volume in 1 second; COPD: chronic obstructive pulmonary disease. DEP: diesel exhaust particle; IL: interleukin; Th2: type II helper T cells; IgE: immunoglobulin E; NK: natural killer cells.

functional imbalance will further disturb lung development and cause air pollutant-exposed offsprings prone to developing respiratory diseases such as asthma and COPD in later life.[141] The genetic variants and decreased expression of antioxidant genes, glutathione S-transferase mu 1 (GSTM1) and coenzyme NAD(P)H quinone dehydrogenase 1 (NQO1) were associated with pollutant-induced exacerbation of allergic and inflammatory diseases in humans.[142,143] The wild-type GSTM1 protein can prevent aggravation of allergic responses by second-hand smoke, while the wild-type glutathione S-transferase pi 1 (GSTP1) protein associated with enhanced nasal allergic responses challenged by DEPs.[129,130]

Structural alterations

Structural changes more likely put a long-term effect of environmental exposure on respiratory diseases. The altered tissue structures and cellularity may last a longer period to reprogram respiratory functions. From animal studies, prenatal exposure to nicotine and maternal smoking caused abnormalities in lung development, including airway branching and dimensions. Continuous epithelial-cell growth and lung branching can be stimulated by prenatal nicotine exposure and result in longer and more torturous airways, leading to weaker respiratory function.[84,144] These outcomes likely attribute to the molecular interaction of nicotine with α7 nicotinic receptors in mice.[139] Mouse studies have demonstrated that maternal smoking remodeled the airway tissue structures by: (1) increasing collagen deposition around the airways so that airway thickness is enhanced; (2) airway inflammatory responses become more severe in house dust mite (HDM)-challenged model due to the induction of goblet cell hyperplasia and the infiltration of neutrophils and mast cells.[145] Smooth muscle thickness in the airway is a good predictor of altered airway responsiveness and respiratory function in smoke-exposed offspring. In animal studies, alveolar remodeling involving the alteration of smooth muscle is found in association with maternal smoking,[146] and further leads to the increased volume of airway smooth muscle and the deposition of collagen, resulting in a subsequent reduction of airflow, reduced FEV1, and potential increase of airway hyperreactivity.[147] Collagen deposition around the airways is observed also in monkeys[148] with a compromised lung function, suggesting the formation of smaller airways and stiffer

lungs.[149] In humans, maternal smoking is able to cause thicker inner airway wall in the infants suffered from sudden infant death syndrome,[150] suggesting the smoke pollutants contribute to the airway remodeling. Both human and animal studies supported an emphysema-like pathological change with thickening airways potentially due to the deposition of collagen and remodeled alveolar walls with the decreased surface area, lower capillary density, weaker respiratory function, and premature aging.[146,151]

Monocytes, macrophages, and dendritic cells

Inflammatory responses mediated by hematopoietic cells in lung tissues have profound roles in regulating respiratory disease outcomes in asthma, COPD, cancers, and infectious diseases. Different subsets of immune cells are potentially impacted by air pollutants to post a long-term impact on respiratory diseases, although more studies are needed for a better understanding (Fig. 2). It is well known that endotoxin enhances the expression of antigen presenting molecules on airway macrophages and monocytes[152] as used as a common stimulating factor to activate monocyte-derived dendritic cells and macrophages.[153] The exposure to ozone enhances the expression of surface markers involved in innate immunity and antigen presentation on airway monocytes, such as human leukocyte antigen–antigen D related molecules (HLA-DR), the co-stimulatory molecule CD86, the co-receptor CD14 for binding bacterial endotoxin, and the antibody receptor CD16.[154] The upregulation of these molecules will likely further enhance the activation of T cells and monocyte-mediated inflammatory responses. The functional upregulation of alveolar macrophage was shown in mouse acute lung inflammatory responses to carbon nanotube exposure.[155] However, it remains poorly understood how innate immune responses in maternal exposure are translated to the impact on fetal lung development.

$CD4^+$ T cells and cytokines

In response to the allergen and other environmental particles, dendritic cells can be activated[156] to induce a type II helper T cell (Th2)-dominant immune response.[157] The Th2-skewed response, as a regulatory mechanism in placenta and pregnancy, is interestingly connected to the adverse response caused by environmental pollutants, such as ozone that enhances Th2-skewed pulmonary inflammation in a rat pregnancy model.[158] A Th2-mediated interleukin (IL)-13 production was indicated to enhance the allergic IgE level, in contrast to the monocyte function represented by CD14 gene expression. In tobacco smoke-influenced atopy in Dutch cohorts, the minor alleles of the IL-13 gene were significantly associated with elevated IgE levels and an increased risk of allergic sensitization in children, but minor alleles from the CD14 gene were associated with lower IgE and a decreased risk of allergic sensitization.[159] As an organic air pollutant released from some manufacturer products such as polyurethane foam,[160] the respiratory and skin sensitizer toluene diisocyanate (TDI) was known to induce a Th2 response.[161,162] In animal studies, application of TDI to mothers led to an enhanced respiratory allergy induced by OVA in offsprings.[162] Further sensitized by allergens and aerosol challenge, the offsprings developed an increased Penh values, airway hyperresponsiveness, in which eosinophils and Th2 cytokines become unbalanced.[161] Specifically, IL-13 but not IL-4 cytokine is required for allergic inflammation in the lung,[163] supporting an exacerbating impact of TDI on lung allergic inflammation. In addition to the vapor forms of air pollutants, particulate pollutants DEPs containing both carbon cores and pollutant chemicals on the surface (Fig. 1) may have an adjuvant effect to protein allergens in humans[31] and in rodents. Repeated exposure to low dose-DEP seemed resulting in an increased airway hyperresponsiveness and inflammatory cytokine expression,[164,165] while continuous exposure to DEP rapidly minimized this effect. Interestingly, the carbon particle cores without the surface organic pollutants also show a pro-asthmatic effect transferred from maternal exposure.[165] In BALB/c mice treated with carbon black particles, lung inflammation in offsprings in responses to maternal exposure of inert particles is enhanced. The limited data virtually supported a disruption of the balanced of $CD4^+$ T cells by multiple air pollutants, contributing to either hyperresponsiveness or pro-inflammatory alterations in respiratory pathology.

Innate lymphoid cells (ILCs)

ILCs are the newly identified family of innate immune cells, which lacks the antigen specific receptors unlike conventional T helper cells. ILCs can secrete various cytokines, including IL-5, IL-13, IL-17, and interferon (IFN)-γ, including multiple common cytokines produced by $CD4^+$ T cells.[166,167] Due to their innate-like characteristics, ILCs are expected to more promptly respond to environmental factors and show different responding kinetics compared to T cells. ILCs have been reported to contribute to the respiratory diseases such as asthma.[167–169] Recent studies in mice have

shown that ILCs can be influenced by air pollutants to exacerbate the respiratory symptoms. For example, DEP-enhanced allergic airway inflammation can be attenuated by reduced number of functional ILCs with suppressed expression of the transcription factor GATA3, which promote the production of Th2-like cytokines.[170] The other studies also showed important role of ILCs to mediate airway hyperresponsiveness induced by pollutants, such as O_3 and multi-walled carbon nanotubes (MWCNT).[171,172] Whereas many functions of ILCs are unknown yet, accumulated evidence suggests a crucial role of ILCs to be further investigated in air pollution-exacerbated respiratory diseases.

Immunoglobulin E (IgE)

Particulate form of air pollutants has been shown to interestingly impact on the production of immunoglobulins in allergic responses. DEP was found to promote antibody production to neoantigens (keyhole limpet hemocyanin, KLH) with a mixed IgE and IgG responses. The production of IgE can be upregulated by Th2 cytokines, such as IL-4.[173–176] Interestingly, oxidative stress is also linked to an enhanced IgE response in environmental exposure, as supported by the observation that DEP-induced oxidative stress initiates a primary IgE response to subsequently encountered allergen based on the evidence of the inhibitory function of thiol antioxidants.[177] Consistent to the role of oxidative stress in inducing a higher IgE response, the null mutation of anti-oxidant gene GSTM1 contributes to a larger increase of IgE in the exposure to air pollutants. PAHs also enhance the allergic responses to cockroach allergen, especially further augmented with the GSTM1 null genotype as in a study with New York urban population.[119] A similar effect was also observed in GSTM1 null children in an exposure to second-hand tobacco smoke for the occurrence of asthma and wheeze symptoms.[132] It remains far from full understanding of immune regulatory mechanisms. Immune pathways impacted by air pollutants may be previously known or unknown mechanisms, contributing to new discoveries of early environmental origins in respiratory diseases.

Epigenetics

Air pollutants may overwhelmingly influence the epigenetic regulators that determine the processes of DNA replication and transcription. The overall impact of environmental pollutants on DNA methylation has been comprehensively reviewed.[77,178–180] At a prenatal stage, mother and fetus are both exposed to air pollutants in different microenvironments (Fig. 2). Mothers are exposed to air pollutants through airway inhalation and body fluid transferring. Fetuses are exposed to air pollutants through the cross-placental transfer of the original or metabolized molecules of air pollutants. Although indirect passage of maternal epigenetic alteration to the fetus is possible, perhaps the direct epigenetic changes in fetus contribute more significantly to the later stage of respiratory diseases. The epigenetic alteration induced by pollutants usually includes DNA methylation and histone modification, which may carry through a long period[181] and determine the initiation of gene expression through selective activation or inactivation of genes. The epigenetic regulation further contributes to controlling immune cell differentiation, inflammatory responses, cell growth, and apoptosis. In respiratory diseases, altered DNA methylation[182,183] is associated with the increased risk of childhood asthma related to maternal smoking,[184] stress,[185] and COPD.[35] As an intensively investigated exposure model, tobacco smoking impacted DNA methylation in children, as shown with global and gene-specific methylation patterns in buccal cells from 348 to 272 children respectively. As a result, significant hypomethylation was observed in prenatal tobacco smoke at a DNA repetitive element, which is a marker of global DNA methylation. This observation is consistent with the protective function of GSTM1 supported by higher methylation in those children with GSTM1, but lower methylation in GSTM1 null children. However, methylation patterns are usually tissue- and cell-specific, as this may impact data interpretation in gene regulation.[186] Besides DNA methylation, an increase of microRNA has also observed in a human acute challenge with ozone and exposure to ambient particulate pollutants.[187–190] Some microRNA such as mi-223 in both infant and maternal monocytes is associated with *in utero* exposure to tobacco smoke.[191]

Epigenetic regulations are involved in the differentiation of Th1, Th2,[192,193] and regulatory T (Treg) cells. For example, epigenetic regulation of the expression of the transcription factor Foxp3 determines Treg differentiation.[194,195] In a mice study, inhaled DEP exposure and intranasal *Aspergillus fumigatus* infection induced hypermethylation at the IFN-γ gene promoter and hypomethylation at the IL-4 promoter. This altered CpG methylation pattern of IFN-γ and IL-4 promoters mediated the differentiation of Th2 cells *in vivo* and correlated significantly with increased IgE production.[196] The impact of trafficked air pollution and

tobacco smoke has been shown on multiple immune regulatory genes, including Toll-like receptors (e.g., TLR2), multiple cytokines (e.g., IL-6, and IFN-γ, IL-4 as noted), nitric oxide synthase (NOS), and various transcription factors (e.g., Foxp3 and Runx3).[178] The long-term effect of these early induced epigenetic alterations on the later onset of respiratory diseases remains elusive.

Conclusions and remarks

Air pollution increases the risk of respiratory diseases, such as asthma, respiratory infections, and COPD, in children and adults. Maternal exposure to air pollutants mediates both short-term and long-term effects on the respiratory system. As described, extensive epidemiologic and meta-analysis studies showed the association between prenatal air pollution exposure and the adverse birth outcomes, including preterm birth, intrauterine growth restriction, low birth weight, pregnancy loss, and defective fetal lung development. The maternal exposure and disorders further impact on fetal lung functional and structural development, leading to various late onset respiratory diseases. Abnormal lung development, disrupted immune responses, and altered epigenetic regulations were suggested as potential underlying mechanisms. Both comprehensive and in-depth mechanistic investigations are required for better understanding of causative pathways in the environmentally induced late onset of respiratory diseases.

Conflicts of interest

All authors have no conflicts of interest to disclose. The authors alone are responsible for the content and writing of the paper.

Acknowledgements

This work was supported by National Institute of Environmental Health Sciences (ES006096), Center for Environmental Genetics (CEG), and National Institute of Allergy and Infectious Diseases (AI115358).

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Edited by Yang Pan and Zhen-Wei Zhang