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The respiratory impacts of air pollution in children: Global and domestic (Taiwan) situation

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ABSTRACT

Air pollution is a global issue that threatens the health of human beings. Epidemiologic reports have shown air pollution exposures to result in millions of deaths annually. Infancy and childhood, the period of organ and lung development, is most susceptible to these environmental hazards; as a result, the risks of respiratory diseases are increased after air pollution exposure. These pollutants can originate from indoor and ambient environment, presenting as vapor or particles, and differ in chemical compositions. This review will give brief introduction to various major pollutants and their origin, as well the correlation with respiratory diseases after exposure. We will also present several current facts in domestic area (Taiwan), regarding the status of local air-pollution, and discuss its impacts on pediatric respiratory health. This report will provide useful information for clinicians and offer advice for policy makers to develop public health guidelines of pollution control and prevention.

Breathing clean air is a basic human right. However, air pollution has become a major global threat to human health and well-being. The global increase in the prevalence of asthma and chronic obstructive pulmonary disease (COPD) has motivated the scientists to further investigate the role of environmental contaminants, focusing especially on air pollution. Recent studies have shown aggravation of respiratory health after exposure to air pollution. Furthermore, according to the assessment of WHO, 9 out of 10 people worldwide breathe air containing high levels of pollutants, which resulted in around 7 million deaths every year from exposure to polluted air, of which 660,000 were children. Ambient air pollution alone caused some 4.2 million deaths in 2016, while indoor air pollution from burning biomass fuels (BMF) has caused an estimated 3.8 million deaths in the same period [1].

Since most alveoli develop postnatally and lung function continue to mature throughout adolescence, children are more susceptible to the adverse impacts of air pollution than adults.

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Children also have higher exposure to air pollution than adults, since they have relatively higher minute ventilation, physical activity, and spend more time outdoors [2]. These respiratory effects during early life from air pollution can persist to adulthood and increase the risk of adult respiratory diseases.

The time children spent in outdoor or indoor environment is closely related with their age [3]. Younger children or children with dysmotility usually spend more time indoors. In contrast, healthy children near school-age usually stay more time in outdoor environment. Therefore, the influences of indoor or ambient air pollution can vary in children with different ages and motility.

This review will focus on the respiratory effects of air pollution on the pediatric population and discuss the domestic situation and reports of various published data.

Air pollutants

Indoor air pollution such as BMF can originate from cooking and heating devices, tobacco smoking, plastic and wood particles, mite, molds, and virus etc. Ambient outdoor air pollution derives mostly from traffic-related air pollution (TRAP). These pollutants are formed primarily by emitting into the air, or secondarily formed within the atmosphere itself [4]. Air pollution consists of a dynamic mixture of many compounds, generated from sources of nature and human activities. Its composition varies between different locations and origins. Since it is difficult to monitor each component of the air pollution mixture, studies usually focus on distinct groups known as "indicator pollutants" (Table 1). The first consists of particulate matter (PM), including PM_{10} (particles smaller than 10 μm), and $PM_{2.5}$ (particles smaller than 2.5 μm). In general, PM_{10} can reach the respiratory airway below the larynx, $PM_{2.5}$ is able to access respiratory bronchioles, alveoli, and even penetrate into the gas-exchange interface of the lung.

Nitrogen oxide (NO_x) is a side-product of oxidation in the atmosphere. NO_x is derived from nitrogen monoxide, a direct combustion product after reacting with oxygen. Thus, it is one of the major components of TRAP. Sulfur dioxide (SO_2) also derives from the combustion reaction of fuel containing sulfur, such as coal and oil. SO_2 can form acid if dissolves in water droplets. It also can interact with other gas to form sulfate, and even coats on PMs to form respirable particulates.

Ozone (O_3) is formed from ambient reaction between nitrogen oxide and reactive hydrocarbons, both emitted from motor vehicles and industrial activities. This reaction is catalyzed under sunlight exposure, so the levels tend to peak during warm, sunny mid-afternoon. Carbon monoxide (CO) is the product of incomplete combustion of BMF. Although the ambient emission of CO has declined significantly after the introduction of catalytic converter for motor vehicles [5], the indoor level can stay high in heated home or cooking with BMF under poor-ventilated environment.

Susceptibility and routes of exposure in children

Lung development begins at the end of the first month of gestation. The process is divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar stages [6]. The process of new alveoli formation is critical for the growth of lung and the development of lung function. Therefore, exposure to hazardous materials during this period has critical effects on the developing fetal lung. These insults may retard fetal lung growth, reduce postnatal development of lung function, and results in unfavorable consequences later in life [7]. There are several studies demonstrating adverse effects of air pollution on pregnancy outcomes [8,9]. Results suggest that the exposure to air pollution during specific windows of lung growth may have particular impact on prenatal development and postnatal performance [10].

In cause of physiological, behavioral, and socio-environmental factors in children, the routes of exposure to air pollutants are different from adults. Children have higher metabolic and breathing rate, and enhanced oxygen consumption per unit of body mass. Besides, children are so short that they breathe in more air pollutants heavier than air [11]. In

Table 1 Major air pollutants.

Pollutants	Sources	Effects	Release
Particulate matter (PM)	*Indoor*: cooking using BMF, cigarette smoking *Outdoor*: natural dusts, vehicles exhaust, industrial activities, constructions.	PM can reduce visibility and cause a variety of respiratory problems. PM has also been linked to cancer and other systemic diseases.	Direct and formed in air
Nitrogen oxides (NOx)	BMF Combustion, vehicles exhaust, industrial activities, power plants. Nitride is the product of nitrogen oxide photochemical reaction.	NOx can make individuals vulnerable to respiratory infections, lung disease, and possibly cancer. It contributes to the brownish haze seen over congested areas and to acid rain.	Direct
Ozone (O_3)	BMF Combustion, vehicles exhaust, industrial activities (photochemical reaction between nitrogen oxides and reactive hydrocarbons).	Ozone can cause irritation of airways, and cause airway hyperresponsiveness and bronchospasm. Repeated exposure can cause permanent lung damage.	Formed in air under sunlight
Carbon monoxide (CO)	BMF incomplete combustion, wood burning, cigarette smoking, vehicles exhaust, industrial activities, forest fire.	CO interferes with the oxygenation of hemoglobin CO can cause death in high concentration.	Direct
Sulfur dioxide	BMF Combustion, coal-burning power plants, volcanic gas.	SO_2 easily dissolves in water and forms an acid which contributes to acid rain.	Direct

Abbreviation: BMF: biomass fuels.

addition, pica behavior and spending more time playing outdoors also predispose children to have higher exposure rate. Thus, the type and amount of exposure differs from that of adults. As for indoor pollutants, small young children can be exposed to higher amount of BMF pollutants as they are usually carried on their mother's back during cooking. People of low socioeconomical area or developing/undeveloped countries usually use wood BMF or cooking in poor ventilated environment, thus, further aggravate the effect of air pollution.

Exposure assessment

Exposure assessment of individuals is to investigate the amounts of pollutants during a certain period of time, which can be a big challenge for epidemiological studies of air pollution. Ideally, continuous monitoring of individual's exposure is the golden standard for determining the effects of pollutants in total amount and real-time concentration. However, it is impossible and impractical to employ this method to large population, since it is difficult to enroll enough participants to fulfill the statistical requirement. Therefore, a variety of modeling methods have been developed to evaluate the effects of exposure in epidemiological studies [12]. Two of the most frequently used modeling methods are the land-use regression (LUR) and the line dispersion model.

The LUR model uses geographic information system (GIS) to obtain the features of environments, and further estimate the spatial variation in exposure of pollutants [13]. This approach applies the measured levels of pollutants at a particular location as the dependent variable, and uses GIS features (e.g., traffic, meteorology, and topography, etc.) as independent variable in multivariate regression model. It can further compute and predict the spatial and sequential variation of pollutants-exposure in a specific area.

Dispersion models largely apply Gaussian plume equation, describing the dynamics and transport within pollutant plume, and computes the pollution levels for the chosen time interval. To fulfill the model consumptions, this model needs to input data on pollutant emissions, meteorology, topography, and other parameters to estimate the levels of pollutants. Data of pollutant emissions and information on meteorological changes (including wind speed, solar radiation, temperature variation, and atmospheric pressure change, etc.) can all be collected from government reports. Recently, GIS also has been intergraded into the topographic information.

These two models are usually appliable in ambient air pollution, but only have limited usage in the study of indoor air pollution. In studying the population of urban young children, who spend most of their time indoors, an extensive assessment model should be developed and adopted to include both indoor and outdoor exposure [14].

Effect of exposure on respiratory health

Asthma

Asthma is characterized as chronic inflammation of the airway. It is clinically associated with airway hyperresponsiveness and reversible airflow limitation. Several observational and epidemiological studies have shown that air pollution is associated with acute exacerbations of asthma [15]. Among ambient pollutants, ozone can cause airway inflammation and significant decline in lung function [16], leading to increased episodes of asthma exacerbation in children [17]. Furthermore, exposure to high amounts of SO_2 and NO_2 can also increase asthmatic episodes in children [18,19]. According to the experiences from the Summer Olympics, aggressive intervention measures, such as decreasing the production of TRAP by restriction of motor vehicles, had remarkably reduced the rate of asthma visits during this period of Olympics Game [20,21].

To investigate the relationship between asthma and air pollution, more complex and delicate cohort study approaches are necessary. Meta-analysis of birth cohort studies showed that longitudinal exposure to ambient pollutants (including NO_2, $PM_{2.5}$, and black carbon) increased the incidence of asthma in young children till 12 years of age [22], and this association is most prominent for $PM_{2.5}$. However, this study was not able to offer any potential explanations for the causative mechanism as there was no significant rise in the prevalence of atopic sensitization (including indoor, outdoor and food allergens).

Contrary to the significant relationship between ambient pollution and asthma, the association between asthma and indoor pollutants remained inconsistent. Regrading to indoor tobacco exposure, maternal smoking in pregnancy was related with increased risk of developing asthma during the first 7 years of life [23,24]; however, direct exposure during the first year of life showed no significant risk [24]. Moreover, a recent meta-analysis found no significant association between asthma and exposure to indoor BMF [25]. Thus, currently, there is no definitive evidence to support the connection between asthma risk and household using BMF.

In summary, air pollution can indeed increase the incident of asthma exacerbation in children. Although prenatal exposure to air pollution can increase the risk of developing asthma in children, the relationship between postnatal or early life exposure and asthma development still requires further investigation.

Respiratory infection and tuberculosis

The association of increased risk of lower airway infection and indoor smoke exposure was first suggested in Nepal's study [26]. By measuring the level of PM_{10}, Ezzati's study showed a significant relationship between the risk of acute respiratory infection and exposure to indoor BMF combustion [27]. A meta-analysis further demonstrated that indoor usage of BMF resulted in nearly 1.8-fold increase in the risk of pneumonia in children aged under 5 years [28].

Similar findings were also found in the exposure of ambient TRAP. Barnett's study showed a strong and consistent association between episodes of pneumonia and outdoor air pollutants (esp. NO_2) in the urban cities [29]. A Spanish study has shown that exposure to NO_2 during the period of pregnancy and first year of life was associated with increased risk of respiratory tract infections (both upper and lower airway) in infants [30]. A recent meta-analysis including 10 European birth cohorts (European Study of Cohorts for Air Pollution

Effects; ESCAPE) clearly demonstrated ambient TRAP, including NO_2 (*OR* = 1.47), PM_{10} (*OR* = 1.77), and $PM_{2.5}$ (*OR* = 4.06), all have close association with the risk of pneumonia in the first year of life [31].

The prevalence of tuberculosis is closely associated with the socioeconomic and industrialization status; therefore, the prevalence would be higher in metropolitan area, where exposure to pollutants of TRAP is greater. A study conducted in urban area of China has shown exposure to high ambient air pollution concentration to increase the risk of tuberculosis, especially in children [32]. Similarly, a case-control study in South Africa showed an increased risk of childhood tuberculosis due to higher use of indoor BMF [33]. Recently, Lee's meta-analysis study has further confirmed that household air pollution significantly increased the risk of infection with tuberculosis (RR = 1.26) [34]. In general, exposure to air pollution (ambient and indoor) has shown strong evidence in increasing the risk of respiratory tract infections and tuberculosis in children, especially those under the age of 1 year.

Abnormal lung function

Prenatal tobacco smoking exposure was associated with decreased lung function in children during school-age [35]. Maternal exposure to ambient TRAP, such as NO_2 particulate matter (PM_{10} and $PM_{2.5}$) also have negative impact on children's health from infancy to school-age period [36–39]. Using the measurement of exhaled NO and infant lung functions testing, Latzin's study has shown that prenatal exposure to ambient air pollution was associated with airway inflammation and higher ventilatory demand [38].

Regarding to the effects of TRAP on the evolution of pediatric lung function, the Southern California Children's Health Study has already presented an extensive cohort investigation. This study showed a negative dose–response influence of ambient air pollutants (NO_2, PM_{10}, and $PM_{2.5}$) on lung function in school-age children [40]. Similar trends were found in the studies conducted in UK and Austria [39,41]. Recently, by investigating the relationship between DNA methylation and NO_2 exposure, an adult cohort disclosed the possible mechanism underlying the connection between air pollution and reduction of lung function [42]. Furthermore, interventions to diminish exposure of air pollution, such as improving ambient air quality or relocating to areas with lower air pollution, has shown significant improvement in lung function growth in adolescents [43,44]. Overall, both prenatal and postnatal exposures to air pollution have negative impact on lung function in children.

Chronic obstructive pulmonary diseases (COPD) in later life

COPD is a heterogenous disease that is characterized by progressive airflow obstruction and destruction of lung parenchyma, usually caused by prolonged exposure to noxious particles or gases. Indeed, poor lung function and persistent respiratory illness in early life may increase the risk of developing COPD later in life [45]. This concept implies that exposure to air pollution during early life (childhood, infancy, or even *in-utero*) might result in pathophysiological change of COPD later in adulthood.

Evidence from several meta-analysis had shown prenatal exposure to air pollution during pregnancy to increase the risk of having low birth weight offspring [46,47]. Exposure to air pollution during early postnatal life can also cause delayed somatic growth, which persisted even to the pre-adolescence period [48,49]. It is plausible that childhood stunting has negative impact on early lung development, which might have been contributed to frequent respiratory illness and subsequent development of COPD [7]. However, several studies did not adequately control for socioeconomic confounding factors, thus, making it difficult to confirm the cause–effect relationship between air pollution and COPD development.

Current status of domestic area (Taiwan)

Because of increasing dense-population and industrialization, the air quality has worsened in most urban area of Taiwan in the last decade. After several attempts of monitoring air quality (Table 2) and interventions of setting new regulation by Taiwan Environmental Protection Administration, the quality of ambient air has improved significantly thereafter, as evidenced by downward trends of various major pollutants

Table 2 Air quality index (AQI).

AQI	$PM_{2.5}$ (μg/m^3) 24 h	PM_{10} (μg/m^3) 24 h	O_3 (ppm) 1 h[a]	O_3 (ppm) 8 h	NO_2 (ppb) 1 h	CO (ppm) 8 h	SO_2 (ppb) 1 h
Good (0–50)	0.0–15.4	0–50	–	0–0.054	0–30	0–4.4	0–20
Moderate (51–100)	15.5–35.4	51–100	–	0.055–0.070	31–100	4.5–9.4	21–75
Unhealthy for sensitive group (101–150)	35.5–54.4	101–254	0.125–0.164	0.071–0.085	101–360	9.5–12.4	76–185
Unhealthy (151–200)	54.4–150.4	255–354	0.165–0.204	0.086–0.105	361–649	12.5–15.4	186–304[c]
Very unhealthy (201–300)	150.5–250.4	355–424	0.205–0.404	0.106–0.200	650–1249	15.5–30.4	305–604[c]
Hazardous (301–400)	250.5–350.4	425–504	0.405–0.504	[b]	1250–1649	30.5–40.4	605–804[c]
Very hazardous (401–500)	350.5–500.4	505–604	0.505–0.604	[b]	1650–2049	40.5–50.4	805–1004[c]

[a] Areas are generally required to report the AQI based on 8-h ozone values. However, there are a small number of areas where an AQI based on 1-h ozone values would be more precautionary. In these cases, in addition to calculating the 8-h ozone index value, the 1-h ozone value may be calculated, and the maximum of the two values reported.

[b] 8-hour O_3 values do not define higher AQI values (≥301). AQI values of 301 or higher are calculated with 1-h O_3 concentrations.

[c] 1-hour SO_2 values do not define higher AQI values (≥200). AQI values of 200 or greater are calculated with 24-h SO_2 concentrations.

(CO, NO_2, SO_2, PM_{10} and $PM_{2.5}$) [50,51]. However, because of local anthropogenic emission and short-term modulation of haze episodes from China, local ambient air quality still fluctuated because of these events [51].

Similar to foreign studies, domestic reports have also shown ambient air pollution and meteorological factors to be closely associated with acute exacerbations of children with asthma [52]. Furthermore, lifetime exposure to air pollutants, especially PM_{10}, is related to the reduction of lung function in non-asthmatic school-aged children [53]. Using spatiotemporal analysis, a significant high relative rate of respiratory clinical visits is also found in areas with high $PM_{2.5}$ concentration, namely highly populated areas [54]. It is shown that by effectively restricting the sources of air pollution and improving the air quality by one-unit reduction in air quality index can result in 7.4 million US dollars saving in respiratory-related outpatient spending per year [55].

Regarding the association between asthma genesis and air pollution, Jung's study disclosed the susceptible time windows in the development of pediatric asthma [56]. This birth cohort in Central Taiwan showed that prenatal and postnatal exposures to $PM_{2.5}$ were associated with subsequent development of asthma in childhood. The vulnerable time windows to exposure being gestational week of 6–22 in utero and 9–46 weeks after birth. The authors thus declared that sensitive population, including pregnant women and young children, should avoid the exposure to ambient air pollution during these susceptible periods.

Need for future investigations

Role of epigenetic modulation

The effects of environmental pollutants on DNA methylation have been systematically reviewed [57]. Methylation of DNA is a cell-type specific pattern with static and dynamic process; consequently, exposures to environmental substances may mediate alterations to DNA methylation. The methylation might in turn enhance inflammation, increase the risk of respiratory, cardiovascular, and metabolic diseases. Air pollution can affect DNA methylation, which might occur during prenatal (in utero) or postnatal (childhood, adolescence, even adulthood) period. It remains unclear if the development of diseases was caused by accelerated process due to early life exposure or simply because of cumulative exposures. Further investigation will be needed to improve the knowledge of how DNA methylation (exposure-induced) impacts on both short-term and long-term respiratory health.

Link of exposures of air pollution and origins of diseases

The concept of the Development Origin of Health and Disease (DOHaD) has been advocated to demonstrate the inextricable link between early-life factors and the risk of developing later-life diseases. Although several studies showed close relationship between exposures to air pollutants and the development of respiratory diseases, the true nature of the link is unclear. More longitudinal birth cohorts will be needed in order to apply better measurements of respiratory function in infants and biomarkers of impact, so to facilitate tracking of the link between exposures of air pollution and development of respiratory diseases.

Effects of intervention in improving air quality

Previous studies have discovered that by improving ambient air quality or relocating to areas of lower air pollution was associated with enhanced lung function growth in adolescents [43,44]. However, the therapeutic effect of improving air quality after aggressive intervention still lacks direct strong evidence. Future investigations with well-controlled designs should be performed to link the gap and offer evidence for policy change to reduce current air pollution.

Conclusions

Children, whose lungs are still under develop, are more vulnerable to the hazards of air pollution. Previous epidemiological and meta-analysis studies showed air pollution to increase the risk of respiratory diseases and leads to long-term respiratory deficits or chronic respiratory illness later adulthood. Both global and domestic data urged prompt intervention to improving air quality so to decrease the incidence of respiratory diseases. A delicate understanding of the health hazards of exposures to air pollution in children is required to persuade the authority to reduce air pollution in order to improve children's health. Furthermore, policy to reduce children's exposure to air pollutants should be implemented without delay.

Conflicts of interest

The authors declare no conflicts of interest.

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