Perspective

Outdoor air pollution and the onset and exacerbation of asthma

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Abstract

Exposure to outdoor air pollution has been consistently associated with asthma. In this study, we reviewed the epidemiological studies published within the last 5 years on the association between outdoor air pollution and exacerbation and onset of asthma. A large number of studies have been published within the last 5 years. Short-term exposure to outdoor air pollution is associated with exacerbation of pre-existing asthma, manifested as worsening of symptoms and increasing of asthma-related emergency room visits and hospital admissions. Furthermore, increasing evidence suggests that long-term exposure to outdoor air pollution can result in onset of asthma. Children are more susceptible to outdoor air pollution. Future studies should be conducted to explore the mechanisms underlying the association between air pollutants and onset of asthma, including gene involvement. In addition, disentangling the effect of a mixture of air pollutants and identifying the key components of air pollution will complete the existing evidence. More importantly, a better understanding is required on the future impact of air pollution on asthma under a changing climate.

Keywords: Outdoor air pollution; Particulate matter; Gaseous pollutants; Asthma

Introduction

Outdoor air pollution is a leading risk factor for human health; it contributes to 3.4 million premature deaths according to the 2017 Global Burden of Disease report.1 The global burden of disease attributable to air pollution has been increasing over the past years due to aging of the population, changes in non-communicable disease rates, and rapidly developing industrialization and urbanization in low-income and middle-income countries. Despite the improvement in air quality among developed countries, air pollution is still a major health risk. Substantial adverse health effects even at low air pollutant concentrations have been reported.2

Asthma is a chronic inflammatory disorder of the airways that is physiologically associated with bronchial hyper-responsiveness, reversible airflow limitation, recurrent symptoms of wheezing, chest tightness,
and cough. Asthma is the most prevalent chronic respiratory disease, affecting 235 million people worldwide.\textsuperscript{5,4} The prevalence of childhood asthma, in particular, has been increasing in recent decades.\textsuperscript{5,6} As a classical multifactorial disease, the etiology of asthma is complex and involves both genetic and environmental triggers. The rising prevalence of asthma in recent decades cannot simply be explained from a genetic perspective, as population-level genetic changes require several generations. This increase may be due to changes in environmental factors, including outdoor air pollution.\textsuperscript{7} Epidemiological and clinical investigations have suggested that exposure to outdoor air pollution can induce airway inflammation and hyper-responsiveness as well as oxidative stress, subsequently leading to exacerbations and possibly even onset of asthma.\textsuperscript{7–15}

A large number of observational studies and several meta-analyses have reported positive associations between exposure to outdoor air pollutants and exacerbations of pre-existing asthma.\textsuperscript{7–15} However, the role of outdoor air pollution in the onset or initial development of asthma is unclear. Infants and children are more susceptible to air pollution because of their higher ventilation rates and reduced nasal deposition efficiencies for inhaled particles.\textsuperscript{8,9} Whether and how early-life and childhood exposure to outdoor air pollution could induce asthma is another ongoing research discussion of the topic.\textsuperscript{8,9}

In this scoping review, we primarily focused on the evidence from observational studies on the associations between the exacerbation and incidence of asthma and exposure to outdoor air pollutants, including particulate matter with aerodynamic diameters <10 and 2.5 μm (PM\textsubscript{10} and PM\textsubscript{2.5}), sulfur dioxide (SO\textsubscript{2}), nitrogen dioxide (NO\textsubscript{2}), carbon monoxide (CO), ozone (O\textsubscript{3}), and traffic-related air pollutants (TRAP). Endpoints of asthma exacerbation include an increase in symptoms or, more commonly, asthma-related emergency room visits and hospital admissions. The effect of indoor air pollution on asthma is outside the scope of this review, although it is an important public health issue, especially in developing countries where solid fuels are used most for cooking.

We searched PubMed for articles published between January 1, 2016 and September 30, 2020, using the keyword “asthma,” and any of the following specific terms: “air pollutant,” “air pollution,” “particulate matter,” “ozone,” “sulfur dioxide,” “nitrogen dioxide,” “traffic-related air pollutant,” or “traffic-related air pollution.” We used the reference lists of the recent reports and review articles identified with this search strategy to include relevant publications.

The literature search was restricted to epidemiological studies and articles published in English.

**PM**

PM is a mixture of solid particles and liquid droplets found in the air that originates from natural sources (such as pollen, Asian dust, and volcanic ash), anthropogenic sources (such as industries and vehicles), and atmospheric transformation.\textsuperscript{16} Exposure to PM can lead to oxidative stress, airway hyper-responsiveness, and airway remodeling.\textsuperscript{8,16} The size and components of PM vary according to the sources, which play an important role in the impact of PM on respiratory systems.\textsuperscript{8,16} Coarse PM, which refers to PM with an aerodynamic diameter of 2.5–10.0 μm, is mainly generated by mechanical processes (such as road dust) and consists of metals, carbons, and crustal-related constituents and deposits mainly in the large conducting airways.\textsuperscript{8,16} Fine PM (i.e., PM\textsubscript{2.5}) and ultrafine PM (with an aerodynamic diameter < 0.1 μm) are generated through secondary formation via atmospheric chemistry as well as from direct emissions from combustion sources. They are deposited throughout the respiratory tract, especially in small airways and alveoli.\textsuperscript{8,16}

Short-term exposure to PM has been associated with asthma exacerbation, including hospital admissions and emergency department visits, and symptoms.\textsuperscript{8,12,16–20} An investigation of the global burden of outdoor air pollution on asthma emergency room visits estimated that 5–10 million annual asthma emergency room visits globally in 2015, representing 4%–9% of the annual number of global visits, were attributable to PM\textsubscript{2.5}, whereas 12% of these estimates were observed in China.\textsuperscript{21} A 10 μg/m\textsuperscript{3} increase in the daily concentration of PM\textsubscript{2.5} was associated with an increase in adult emergency department visits by 1.5% (95% confidence interval [CI]: 1.1–1.7) and pediatric emergency department visits by 3.6% (95% CI: 1.8–5.3) in a previous study, suggesting that children can be more susceptible to PM\textsubscript{2.5}.\textsuperscript{22} A large longitudinal study conducted in Paris, France indicated that most of the short-term effects of PM\textsubscript{2.5} that resulted in pediatric emergency department visits due to asthma exacerbation occurred at concentrations below the European Union limit value of 25 μg/m\textsuperscript{3}.\textsuperscript{13} It is likely that the current air quality standard for PM may not provide sufficient protection for children with asthma due to the short-term...
effects of PM. Additionally, the short-term association between PM and hospital admission and emergency department visits has been reported to be stronger during warm seasons. Another issue of interest is related to the possible confounding effects of gaseous pollutants on the short-term effect of PM. Current evidence, however, suggests that the association between PM and hospital admission and emergency department visits is similar even after adjusting for gaseous pollutants.

Instead of using data on PM concentrations from monitoring stations to represent the individual PM exposure level, several epidemiological studies have measured personal PM exposure levels (e.g., residential/school outdoor concentration) and investigated its association with respiratory symptoms in participants with asthma. Although the results of previous studies are inconsistent in some aspects, evidence suggest that PM exacerbates asthma symptoms, especially among children.

Although PM exposure has been linked with asthma exacerbation, its association with the onset and development of asthma is unclear. Some studies have suggested that exposure to PM may result in onset of asthma. Based on a recent systematic review of the association between air pollution and the risk of development of childhood asthma, the hazard ratio of developing childhood asthma was 1.03 (95% CI: 1.01–1.05) for a 1 μg/m³ increase in the annual mean concentration of PM$_{2.5}$. An administrative cohort study involving >1 million children showed a positive association between PM$_{2.5}$ and onset of asthma (hazard ratio: 1.23; 95% CI: 1.21–1.24). However, some studies did not report any significant association between PM and the incidence of pediatric asthma.

**Gaseous pollutants**

Gaseous pollutants include NO$_2$, volatile organic compounds, carbon dioxide, SO$_2$, and O$_3$. Oxidizing gases, especially NO$_2$ and O$_3$, have been associated with asthma because of their oxidative potential leading to oxidative stress. NO$_2$, an indicator of a larger group of nitrogen oxides, is a secondary pollutant mainly from fossil fuel combustion; emissions from traffic can contribute up to 80% of ambient NO$_2$ in cities. The considerably large proportion of NO$_2$ in traffic-related emissions has led to its use as a marker of TRAP. Ground-level O$_3$ is formed by photochemical reactions between sunlight and pollutant precursors, such as nitrogen oxides and volatile organic compounds, and it has a distinct seasonal pattern with peaks during hot seasons. There is substantial evidence on the impact of NO$_2$ and O$_3$ on respiratory systems.

Exposure to high levels of these air pollutants may increase respiratory symptoms and hospital admissions or emergency room visits, especially among people with asthma. It has been reported that 9–23 million and 5–10 million annual asthma emergency room visits globally in 2015 may be attributable to O$_3$ and NO$_2$, respectively, representing 8%–20% and 4%–9% of the annual number of global visits, respectively. China and India, in particular, recorded 23% and 10% of all asthma emergency room visits attributable to O$_3$, respectively. In East Asia, hospital utilization for asthma in children increased by 2.9% (95% CI: 2.2–3.7) and 3.5% (95% CI: 2.5–4.6) for every 10 μg/m³ increase in the concentrations of O$_3$ and NO$_2$, respectively. O$_3$, in particular, has been projected to increase under a changing climate in the future, due to higher temperature and greater solar radiation. There are growing concerns regarding the possibility that O$_3$-related asthma hospital admissions may increase in the context of a warming climate in the future. For example, O$_3$-related asthma emergency department visits in the US were projected to increase to 84,000 per year, with annual costs between USD 45 million and 156 million under the “business-as-usual” climate scenario.

In addition to the short-term effects of NO$_2$ and O$_3$ on asthma exacerbation in adults and children, their long-term effects on onset of asthma have been of great interests over the past decade. Based on 21 birth cohort studies, Khreis et al. reported that childhood exposure to air pollution plays a causal role in the development of asthma. An open cohort of children born in the province of Quebec in Canada reported that hazard ratios for an interquartile range increase in NO$_2$ (5.45 parts per billion [ppb]) and O$_3$ (2.22 ppb) were 1.04 (95% CI: 1.02–1.05) and 1.11 (95% CI: 1.10–1.12), respectively. The annual global pediatric asthma new cases attributable to NO$_2$ was 4.0 million (95% uncertainty interval [UI]: 1.8–5.2), accounting for 13% (95%UI: 6%–16%) of global incidence, and 64% of these occur in urban centers. More importantly, 92% of pediatric asthma incidence attributable to NO$_2$ occurred in areas with annual average NO$_2$ concentrations lower than the World Health Organization guideline of 21 ppb.

SO$_2$ is generated from the burning of sulfur-containing fuel, such as coal or diesel, and can also be converted into sulfate, which is a major contributor to PM pollution. Exposure to SO$_2$ can cause bronchoconstriction, especially in people with asthma. The association between...
SO2 exposure and exacerbation of asthma has been investigated extensively. Given the substantial reduction in SO2 levels in recent decades, the focus on the impact of outdoor air pollution on asthma has shifted from SO2 to other pollutants (such as PM2.5, O3, NO2, and TRAP). However, SO2 pollution is still a key risk factor for asthma, especially in developing countries.32 More importantly, increasing evidence suggests harmful effects on human health even at low SO2 levels.25,36 A meta-analysis on the short-term exposure to SO2 and the mortality of asthma reported that hospital utilization for asthma among children in East Asian countries increased by 5.7% for every 10 μg/m3 increase in the daily mean concentration of SO2.32 Similar to NO2 and O3, SO2 has also been associated with onset of asthma. For example, a population-based birth cohort study in Canada involving 722,667 children reported an increase of 23% (95% CI: 21–24) in the risk of asthma onset in children for a change from the 25th to the 75th percentile in the mean annual SO2 concentration (1.6 μg/m3).6

**TRAP**

In urban areas, TRAP, which comprise a mixture of vehicle exhausts, secondary pollutants, evaporative emissions from vehicles, and non-combustion emissions (such as road dust), is a main source of outdoor air pollution.57 Since it is impossible to measure all the components of TRAP, surrogates have been used to represent TRAP-related exposure.38 The most commonly used surrogates include measured or modeled concentrations of pollutant surrogates, including NO2, CO, elemental carbon, PM, and ultrafine particles, and direct measures of traffic, including proximity/distance of the residence to the main road and traffic volume within the buffer.38

Experimental studies of TRAP using pollutant surrogates have identified increases in asthma-related symptoms and healthcare utilization in association with increases in TRAP (such as NO2 and PM2.5),8 which have been discussed in earlier sections. Using self-reported truck traffic as a surrogate for TRAP, the third phase of the International Study of Asthma and Allergies in Childhood reported that a higher frequency of truck traffic on the streets was related to increases in the prevalence of symptoms of asthma.59

Exposure to TRAP is considered to be associated with the incidence of asthma based on the large body of evidence on the association between pollutant surrogates (e.g., NO2) and the incidence of asthma.8,21,26,34 With increasing urbanization, TRAP exposure and its impact on asthma have been of great interest in research, and there are several global and national estimates and systematic reviews summarizing the existing evidence on this issue.21,34,40,41 However, the results varied between studies. For example, a national Japanese nested case-control study investigated the association between personal exposure to outdoor nitrogen oxides and elemental carbon at home during the first 1½ years of life and the incidence of asthma between the ages of 1½ and 3 years and found no statistically significant association with the incidence of asthma.40 Another cohort study in Korea discovered a positive association between residential proximity to the main road and the incidence of asthma.41

**Recent investigations on air pollution and onset of asthma**

There is a growing body of evidence in the literature on the association between air pollution and onset of asthma.42 However, the current existing evidence is suggestive but not sufficient for a causal relation between air pollution and onsets of asthma. A recent nationwide case-control study in Denmark followed up all Danish children who were born between 1997 and 2014 for onset of asthma from the age of 1 year–15 years and investigated its association with PM10, PM2.5, and NO2.43 This study linked the exposure of children to higher levels of PM2.5 to onset of asthma, with weak evidence for PM10 and NO2.43 Another recent study investigated the association between NO2 and early- or late-onset childhood asthma phenotypes in Canada and reported that children exposed to high levels of NO2 were more than twice as likely to have early-onset asthma, suggesting that the impact of NO2 on the onset of asthma may vary depending on the childhood developmental stage.44 The current findings on the association between air pollution and adult-onset asthma are inconsistent. Exposure to high levels of NO2 has been linked to an increased prevalence of adult asthma in Taiwan, China.45 The multicenter project, titled “Effect of Low-Level Air Pollution: A Study in Europe (ELAPSE),” showed that long-term exposure to PM2.5, NO2, and black carbon was associated with the incidence of asthma in adults, whereas a 15-year population-based cohort study on all Ontarians did not find an association between air pollution and adult-onset asthma.46,47

In general, the recent findings on the association between air pollution and childhood- and adult-onset asthma vary across studies, and this may be related to the differences in genetic factors, indoor/household...
exposure to air pollutants, lifestyle, and diet. In addition, the susceptibility of children to the impact of air pollution may vary with the developmental stages.\textsuperscript{44} and further investigations on the susceptible window should be conducted.

**Research gaps**

Although extensive studies have been conducted to investigate the association between outdoor air pollution and exacerbation and onset of asthma, there are several knowledge gaps on this topic.

The mechanisms underlying the association between air pollutants and onset of asthma are unclear.\textsuperscript{8} For example, the key air pollutants and how different pollutants interact with each other are controversial. Although air quality has improved in several areas, there is an ongoing discussion on the potential adverse health effects of low exposure levels of air pollutants. Future epidemiological and experimental studies are needed to investigate this issue, which will provide critical evidence for the revision of current air quality standards. In addition, the etiology of asthma involves both genetic and environmental factors. Gene—environment interaction is another issue of interest for future research.\textsuperscript{8}

Obtaining a reliable estimate of the effect of air pollutants on asthma requires a proper assessment of the exposure level.\textsuperscript{1} Most of the current observational studies used data on proximity to traffic, measurement data from the monitoring stations, or estimation data from the statistical techniques to represent the individual exposure level to air pollutants, which may have resulted in some bias in the final effects estimates. The exposure window used for studying the association between air pollutants and asthma needs to be further investigated—(1) the appropriateness of the hourly maximum concentration or averaged 24-hour concentration of air pollutants for use for short-term exposure level; (2) the duration of the effect of short-term exposure to air pollutants; and (3) the most sensitive exposure window for developing asthma (e.g., prenatal or early-life exposures).

One of the most challenging issues for environmental epidemiological studies on air pollution and health is how to disentangle the effect of a mixture of air pollutants.\textsuperscript{8} Populations are exposed to a mixture of air pollutants, and the major component, time, and level of exposure to this mixture depend on the time—activity patterns of people. Moreover, it is unclear how air pollutants interact with other environmental triggers (such as second-hand smoking), diet, and other lifestyle-related habits in the development and exacerbation of asthma.

Under a changing climate, the concentrations of air pollutants, such as O\textsubscript{3} and NO\textsubscript{2}, may increase, and a lengthening growing season and increased production of pollen may also increase exposure to allergens.\textsuperscript{33} Therefore, the potential impact of climate change should be considered when investigating and discussing the future impact of outdoor air pollutants on asthma.

**Conclusion**

In summary, studies have suggested that outdoor air pollution is a risk factor for asthma. There is sufficient evidence to link air pollution with exacerbation of asthma. Increasing evidence demonstrates an association between outdoor air pollution and onset of asthma; however, there are some inconsistencies across different studies. Despite a large number of studies on the association between outdoor air pollution and asthma, future studies should be conducted to investigate the underlying mechanisms, improve exposure assessment, and demonstrate the effect of a mixture of air pollutants while considering the potential impact of future warming.

**Conflicts of interest**

None.

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