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Allergic diseases and air pollution

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The prevalence of allergic diseases has been increasing rapidly, especially in developing countries. Various adverse health outcomes such as allergic disease can be attributed to rapidly increasing air pollution levels. Rapid urbanization and increased energy consumption worldwide have exposed the human body to not only increased quantities of ambient air pollution, but also a greater variety of pollutants. Many studies clearly demonstrate that air pollutants potently trigger asthma exacerbation. Evidence that transportation-related pollutants contribute to the development of allergies is also emerging. Moreover, exposure to particulate matter, ozone, and nitrogen dioxide contributes to the increased susceptibility to respiratory infections. This article focuses on the current understanding of the detrimental effects of air pollutants on allergic disease including exacerbation to the development of asthma, allergic rhinitis, and eczema as well as epigenetic regulation.

Key words: Allergy; Air pollution; Tobacco smoke pollution; Environmental exposure

INTRODUCTION

Increasing evidence shows that air pollution is associated with adverse health outcomes, particularly respiratory diseases. Rapid global urbanization and increased energy consumption have exposed the human body to not only an increased quantity of ambient air pollution, but also a greater variety of pollutants. The principle air pollutants of concern are particulate matter (PM), ozone (O_3), and nitrogen oxides (NO_X) in addition to other indoor air pollutants. The detrimental effects of these materials on the exacerbation of asthma as well as respiratory morbidity and mortality in asthma patients are well documented [1, 2]. Evidence that transportation-related pollutants contribute to the development of allergies is also emerging. Furthermore, exposure to PM, O_3, and nitrogen dioxide (NO_2) contributes to increased susceptibility to respiratory infection [3, 4]. Recent advances in the understanding of the mechanisms involved in the association between air pollution and allergies provide insight into how air

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pollution influences the epigenetic alteration of genes [5, 6]. Since many Asian countries have recently industrialized, the use of motor vehicles and production of exhaust gas from factories are rapidly increasing. Additionally, coal is still used as the major source of energy in many Asian countries [7, 8]. This article focuses on the detrimental effects of air pollutants on allergic diseases including exacerbation to the development of asthma, allergic rhinitis, and eczema as well as effects on epigenetic regulation.

Air pollutants and their roles in allergies

Outdoor air pollutants

The major source of NO_2 and PM is fossil fuels, which are combusted by motor vehicles, power stations, and factories (Table 1). Of these, PM production by motor vehicles contributes to a substantial part of air pollution. PM is a general term that refers to tiny fragments of solid or liquid matter associated with the atmosphere, which vary in number, size, shape, chemical composition, and origin. The largest single source of airborne PM from motor vehicles is diesel exhaust [9]. Diesel exhaust particles (DEPs) account for most airborne PM in the world's largest cities because of the increasing number of new cars with diesel engines in industrialized countries [10, 11]. In addition to the increasing sales of diesel vehicles, the fact that diesel fuel combustion results in up to 100 times more particles than gasoline suggests that diesel exhaust may be a significant contributor to increases in the prevalence of allergic diseases. In an animal study, DEP exposure led to increased rates of allergic reactivity and asthma with elevated production of antigen-specific IgE and histamine [12]. Human data show that DEP exposure increases interleukin (IL)-4, IL-5, IL-6, and IL-10 mRNA levels and reduces IFN-γ levels [13, 14]. These results suggest that DEP exposure may be associated with reduced Th1 function.

O_3, a triatomic molecule comprising 3 oxygen atoms, is formed by the action of ultraviolet light and atmospheric electrical discharges (NO_X and volatile organic compounds (VOCs)) on dioxygen. O_3 is a far more powerful oxidant than dioxygen and has many industrial and consumer applications related to oxidation.

Table 1. The principal air pollutants of concern

Pollutant		Sources	Primary standard
Outdoor	PM	Fuel combustion (vehicles, power plants)	15 μg/m3 (annual) 35 μg/m3 (daily)
	O_3	Fuel combustion (cars, power plants, gasoline dispensing facilities)	0.08 ppm (8 h)
	NO_2	High temperature combustion	0.053 ppm (annual)
	SO_2	Industrial processes Coal combustion Petroleum combustion	0.03 ppm (annual) 0.14 ppm (daily)
	CO	Vehicular exhaust Incomplete combustion of fuel (natural gas, coal, wood)	9 ppm (8 h) 35 ppm (1 h)
Indoor	Second-hand smoke		
	Radon	Rock formations beneath buildings	
	CO	Fuel combustion	
	CO_2	Human metabolic activity	
	VOCs	Gases from certain solids or liquids (paints and lacquers, paint strippers, cleaning supplies, pesticides)	

PM, particulate matter; O_3, ozone; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; VOCs, volatile organic compounds.

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Indoor air pollutants

Environmental tobacco smoke (ETS), which is also referred to as passive smoking or secondhand smoke, is the greatest indoor air pollutant. It is defined as the exposure of a nonsmoking person to tobacco combustion products emitted by others. Postnatal exposure to ETS is causally related to the development childhood asthma. Furthermore, ETS is related to an increased risk of adult-onset asthma [15, 16]. Exposure to cigarette smoke reduces Th1 cytokine activities such as those of IFN-γ and NK cells [17, 18]. This reduced Th1 function is linked to a reduced ability to fight respiratory infections and is thought to function in carcinogenesis.

Besides ETS, many indoor building materials, new furniture, and fresh paint may cause allergies [19]. VOCs such as formaldehyde will be discussed in upcoming issue. Perfluorocarbons are used as stains and water repellents applied to furniture fabrics and carpeting. Plasticizers (i.e., phthalates) are compounds added to plastics to make them more flexible. Triclosan is an antimicrobial agent used in soaps, deodorants, toothpastes, shaving creams, and mouthwashes. Organic solvents are used in many industrial and commercial settings as well as in dry cleaning, paint, paint thinner, clues, inks, nail polish, nail remover, and various building and construction materials. These indoor materials are associated with higher rates of allergic and respiratory problems, directing the immune system toward Th2 dominance and suppressing Th1 function [20-23]. Herbicides and pesticides are also strongly associated with asthma and allergies and have been demonstrated to induce Th2-dominant immune responses [24-26].

Air pollution and asthma

Asthma is characterized by airway inflammation and bronchial hyperresponsiveness. The prevalence of asthma has increased rapidly worldwide, particularly in industrialized societies [27]. Many studies have focused on the relationship between air pollution and asthma.

Air pollution and asthma exacerbation

Asthma symptoms can be exacerbated by numerous causes including infection, drugs, excess allergen exposure, and meteorological changes. Many epidemiological studies demonstrate strong associations between air pollution and asthma exacerbation.

NO_2 exposure is linked to emergency room visits, wheezing, and medication use among children with asthma [28, 29]. NO_2 also potentiates allergic responses to specific inhaled allergens in asthma patients [30, 31]. O_3 exposure is also associated with hospital admissions [32, 33], worsening of symptoms, rescue medication [34], asthma attacks, respiratory infections, and reduced peak flow rate [35]. There is substantial evidence demonstrating the effects of particulate pollution on respiratory function [36] and increased asthma symptoms [33]. Ambient sulfur dioxide (SO_2) exposure may also be a risk factor for respiratory symptoms in asthma patients [37, 38]. An animal study demonstrates this association in that repeated exposure to low levels of SO_2 enhanced the development of ovalbumin-induced asthmatic reactions in guinea pigs [39].

Asthma can be exacerbated as a consequence of exposure to the abovementioned air pollutants. The causal relationship between transportation pollution and worsening of asthma symptoms was evident in a randomized crossover study involving 60 volunteers [40]. On separate days, participants walked along Oxford Street, a heavily trafficked street in London, and on another day, they walked Hyde Park, a nearby park with low air pollution levels. Walking along Oxford Street induced asymptomatic but significantly greater reductions in forced expiratory volume in 1 second (FEV_1) and forced vital capacity than walking through Hyde Park.

Many research groups in Asia report concordant results regarding the associations between air pollution and respiratory symptoms. The relative risks of emergency outpatient hospital visits are all positively and significantly associated with interquartile increases for selected lags for all air pollutants in Korea [41]. Similarly, a comparative study found that the prevalence rates of asthma symptoms are significantly higher in Incheon, Korea, which has significantly higher levels of outdoor CO and PM than Jeju, Korea [42]. However, Kim et al. [43] found no such association between air pollutant levels and the relative risk of emergency room visits. The authors state seasonal variation and interindividual differences as the key reasons for the inconsistency with previous studies. In Taiwan, seasonality in air pollutant levels is reported to be associated with asthma admission; moreover, asthma hospitalization propensity is significantly correlated with air pollution levels [44]. $PM_{2.5}$ levels are associated with the percentage of neutrophils and IL-8 level in nasal lavage on the day of exposure [45]. Several researchers in Hong Kong also report evidence corroborating the adverse effects of ambient concentrations of air pollutants on hospitalization rates for asthma [46, 47]. The 2008 Beijing Olympic and Paralympic Games provided a large natural

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experiment showing that significant reductions in the average concentrations of CO, PM_{10}, NO_2, and O_3 [48] resulted in significant reductions in hospital visits due to asthma [49].

Biomarkers of airway inflammation and oxidative stress, such as exhaled breath condensate pH, supernatant IL-8, supernatant myeloperoxidases, and exhaled breath malondialdehyde, were recently used as outcome measures in epidemiological studies [40, 50]. These methods enable a more accurate estimation of individual pollutant level exposure.

Air pollution and asthma prevalence

Although it is well known air pollutants can cause immediate respiratory symptoms, the role of air pollution in the increased incidence of asthma is less clear. However, some researchers postulate the causes of the dramatic increase in the prevalence of asthma and allergic diseases. Furthermore, recent studies provide evidence showing that air pollution is associated with the development of asthma. Many birth cohort studies followed children until preschool age and report a correlation between transportation-related air pollution and asthma onset [51-55].

In China, the number of asthma cases has increased rapidly since the early 2000s [56]. Researchers have published several epidemiologic studies on the association between ambient pollutants and asthma prevalence. Many studies report that the prevalence of bronchial symptoms with asthma is positively associated with NO_X, O_3, and PM levels [37, 38, 57]. In Japan, a prospective cohort study was conducted to confirm the association between the incidence rate of asthma and ambient NO_2 level during follow-up [58]. A study investigating the annual respiratory symptoms of 3,049 Japanese students from 8 urban and rural areas shows a positive association between regional NO_2 levels and asthma prevalence [59]. India's national health survey also identified the influence of pollution from biomass combustion on the prevalence of asthma [8]. However, several studies failed to detect such associations [60, 61]. Furthermore, asthma prevalence is not necessarily proportional to air pollutant levels. Diverse factors including ethnic characteristics should be considered.

Air pollution and other allergic diseases

Air pollution and allergic rhinitis

Two major mechanisms explain the increased prevalence of allergic rhinitis in industrialized areas. Increased fossil fuel combustion may initially lead to allergic sensitization and airway responsiveness to allergens. Airway responsiveness to environmental allergens may subsequently aggravate symptoms of allergic rhinitis [62]. A longitudinal birth cohort study reports that children living near major roads have increased odds of runny nose and sneezing during the first year of life [63] as well as increased odds of sensitization during the first 8 years of life [64, 65]. Similar results were found in Taiwan. A study of 32,143 Taiwanese school children indicates that persistent exposure to NO_X, CO, and SO_2 may increase the prevalence of allergic rhinitis [66]. In addition, transportation-related air pollution is a possible risk factor for allergic rhinitis in middle school-aged children [67].

Air pollution and eczema

In contrast to other allergic diseases, many cohort studies report no association between air pollutants and the incidence or prevalence of eczema [51, 53, 68]. Yura et al. [69] also failed to find a correlation between the ambient air pollution levels and eczema prevalence. A recent study conducted in Korea shows that management in a low-pollutant room significantly reduces the scoring of atopic dermatitis, while PM, formaldehyde, total VOCs, CO, bacterial suspensions, and indoor molds are significantly higher in patients' homes than the low-pollutant room [70]. The authors of the abovementioned suggest that indoor air pollutants are likely to cause atopic dermatitis in susceptible individuals. This finding is concordant with that of the latest study investigating the clinical effects of outdoor air pollutants such as PM, toluene, and VOCs on eczema symptoms using a longitudinal study design with an 18-month follow-up [71]; this study found that atopic dermatitis symptoms are associated with the levels of outdoor air pollutants such as PM, toluene, and VOCs.

Genome and gene-environment interaction

Studying the effects of various air pollutants on respiratory health with respect to an individual's genetic makeup is interesting, given the emerging epidemiological and experimental evidence of their association [72]. Gene and air pollution may have effects on each other. Individual responses to air pollution exposure are determined by genetic differences between subjects, and exposure to air pollution in itself can induce epigenetic changes via methylation.

Genetic predisposition

The large interindividual variation with respect to respiratory

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Table 2. Studies of interactions between genetic predispositions and air pollutants

Genes	Exposed material	Outcome	*p* for interaction	Main findings	Country	References
GSTM1, NQO1	O_3	FVC, FEV_1, PEF, $MEF_{25,50,75}$	< 0.01	*NQO1wt* and *GSTM1null* subjects showed greater ↓ in lung function	Italy	[74]
GSTM1, NQO1	O_3	8-OHdG	< 0.01	*NQO1wt* and *GSTM1null* subjects showed higher ↑ in 8-OHdG*	Italy	[75]
GSTM1, NQO1	Lifetime residence in Mexico City	Asthma	0.013	Carriers of *GSTM1null* and Ser allele for *NQO1* were at ↓ risk of asthma	Mexico	[88]
GSTM1	O_3	$FEF_{25–75}$	< 0.01	*GSTM1null* children had significant ozone related ↓ in $FEF_{25–75}$, and greater ↑ in $FEF_{25–75}$ after antioxidant treatment	Mexico	[77]
GSTM1, GSTP1	DEP	Nasal allergen-specific IgE, histamine, IL-4, IFN-γ	< 0.05	*GSTM1null* patients had a larger ↑ increase in IgE, histamine after DEP plus allergen challenge *GSTP1* I105 genotype was associated with↑in IgE, histamine after challenge with DEP and allergens	USA	[76]
	Outdoor air pollution	Asthma	< 0.035	*GSTP1* I105 genotype in high air pollution district had a ↑ risk of asthma	Taiwan	[86]
TNF	O_3	FEV_1	0.047	*TNF* haplotype comprising *LTA*+ 252G/*TNF*- 1031T/*TNF*- 308A/*TNF*- 238G was associated with the smallest ↓ in FEV1 with ozone exposure	Germany	[89]
TNF–308	O_3	Lifetime wheezing and asthma	0.003	Children with *TNF–308 GG* had ↓ risk of lifetime wheezing	USA	[80]
GSTM1, GSTP1	ETS	Nasal allergen-specific IgE, histamine, IL-4, IFN-γ	< 0.03	*GSTM1null* or *GSTP1* I105 genotypes showed larger nasal responses to allergens with ETS *GSTM1null* subjects had a larger ↑ in IgE *GSTP1* I105 genotype subjects had ↑ histamine	USA	[90]
GSTM1	O_3	Breathing difficulties	< 0.05	*In GSTM1null* or *GSTP1* Val/Val patients, ↑ in breathing difficulty was associated with O_3 exposure	Mexico	[91]
EPHX1, GSTM1, GST P1	Close to major road	Lifetime asthma	< 0.05	High *EPHX1* activity was associated with an ↑ risk for lifetime asthma *GSTP1* 105 Val/Val genotype and high *EPHX1* phenotype had ↑ risk of lifetime asthma	USA	[78]
TGF-β1	Distance to freeway	Lifetime asthma	Not given	*TGF-β1*–509TT genotype is at ↑ risk of asthma when they are exposed to traffic-related emissions	USA	[81]
GSTP1, TNF	NO_2 during 1 year of life	PEF, asthma symptom, specific IgE	< 0.01	*GSTP1* 105 Val/Val and Ile/Val genotypes were at ↑ risk of sensitization to any allergen when exposed to elevated levels of traffic NOx	Sweden	[79]
HMOX1	O_3, PM, NO_2	New-onset asthma	< 0.003	*HMOX1* "short"allele were associated with a ↓ risk for new onset asthma, and this effect was largest in low O_3 area	USA	[92]
ARG1h4	O_3	Lifetime asthma	< 0.05	Carrying the *ARG1* haplotype had ↓ asthma risk among atopic children living in high O_3 communities	USA	[93]
GSTT1	Incense burning	Asthma, wheeze	Not given	*GSTT1 null* genotypes were associated with current asthma and medication use	Taiwan	[87]
GSTM1, GSTP1	SO_2, NO_2, NO, PM_{10}	Intraday variability in FEV_1	Not given	Neither *GSTM1* nor *GSTP1* genotypes alone were associated with intraday variability in FEV_1	South Africa	[94]

O_3, ozone; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; $MEF_{25,50,75}$, maximal expiratory flows at 25%, 50%, and 75% of vital capacity; FEF_{25-75}, forced maximal mid-expiratory flow; DEP, diesel exhaust particulate; ETS, environmental tobacco smoking; NO_2, nitrogen dioxide; PM, particulate matter; NO_2, nitrogen dioxide; SO_2, sulfur dioxide. *8-OHdG, 8-Hydroxy-2-deoxyguanosine: a biomarker of ROS–DNA interaction.

response to air pollutants (i.e., the airway inflammation and oxidant pathway) is known to be genetically regulated. Several candidate gene studies have focused on polymorphisms in genes involved in antioxidant stress and inflammation [73]. Polymorphisms in the genes encoding the following enzymes involved in oxidative stress response have been studied: GST, CAT, SOD, GPX1, NQO1, HMOX1, and EPHX1.

Studies on the interaction between genetic predispositions and air pollutants are presented in Table 2. Subjects with susceptible genotypes (i.e., polymorphic NQO1 and GSTM1) exposed to O_3 during exercise exhibit greater decreases in FEV_1 [74] as well as a modified lung response to O_3 [75] as compared to those without the susceptible genotypes. GSTM1 and GSTP1 polymorphisms alter the response to combined exposure to pollen and DEPs [76]. Furthermore, children with asthma with a genetic deficiency of GSTM1 are more susceptible to the deleterious effects of O_3 and derive greater benefit from antioxidant supplementation [77]. With respect to the effects of air pollution, GSTP1 polymorphisms are also associated with a greater risk of asthma [78] and sensitization to allergens [79].

Besides genetic variation in the extent of oxidative stress, polymorphisms in inflammatory genes have been examined. The TNF-308 GG genotype exerts a protective effect on lung function against O_3 exposure [80], while TGF-b1 increases the risk of asthma in children living near major roads [81].

Epigenetic regulation of gene expression

Epigenetic mechanisms such as DNA methylation may contribute to gene–air pollution interactions. Exposure to environmental agents such as cigarette smoke and air pollutants induces changes in DNA methylation [5, 82]. Prenatal cigarette smoke exposure leads to the hypomethylation of repetitive elements and alterations in gene-specific methylation [83]. One animal study reports epigenetic changes after DEP exposure [84]. In that study, DEP inhalation by BALB/c mice sensitized to Aspergillus fumigatus resulted in hypermethylation of the IFN-γ promoter and hypomethylation of the IL-4 promoter in $CD4^+$ T lymphocytes, leading to altered IgE production. Sofer et al. [85] report that exposure to black carbon and sulfate are significantly associated with the methylation pattern in the asthma pathway, suggesting that the effect of air pollution on airway responses may be mediated through gene methylation. Only a few published studies in Asia [86, 87] have examined the effect of gene–environment interactions for determining susceptibility to asthma and allergies. Future studies on candidate genes for reversing the deleterious oxidizing effect of air pollution to clarify the precise roles of air pollutants on asthma and allergies are warranted.

CONCLUSION

Although the causative role of air pollution in the development of allergic diseases remains controversial, several epidemiological and experimental studies indicate that air pollutants play roles in both the initiation and exacerbation of allergic diseases. Physicians should be aware of the importance of air pollution in allergic diseases and work with their communities to control air pollutants not only to prevent the exacerbations and development of allergic diseases, but also to improve people's health worldwide.

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