INFLUENCE OF AIR POLLUTION ON RESPIRATORY DISEASE

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ABSTRACT

A large number of individuals live in areas of poor air quality, especially in urban environments. Such residency is linked with the exacerbation of asthma, respiratory morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD), and increased risk of viral respiratory infections. Recent studies, again particularly in urban areas, suggest a role for air pollution in the development of both asthma and COPD. In cities the major pollutant of concern is particulate matter (PM), which in both Europe and North America arises mostly from traffic, while in Asia biomass combustion also makes an important contribution. No matter the source, PM exposure can give rise to oxidative stress in the airways. Recent advances in understanding the mechanisms implicated in the association of air pollutants and airway disease include epigenetic alteration of genes by combustion-related pollutants and how polymorphisms in genes, involved in antioxidant pathways and airway inflammation, can modify responses to air pollution exposures. Other interesting epidemiological observations related to the increase of host susceptibility include a possible link between chronic PM exposure during childhood and vulnerability to COPD in adulthood, and that infants subjected to higher prenatal levels of air pollution may be at greater risk of developing respiratory conditions. As medical research continues to expand links between air pollution and an increased incidence and/or severity of airway disease, there is an ongoing need for policy initiatives to improve air quality. Furthermore, accessible, easy to interpret, and engaging information systems are needed to help individuals with respiratory conditions to make informed choices about their behaviour, in a way that improves their health as well as the quality of the air they breathe.

Keywords: Particulate matter, nitrogen dioxide, ozone, asthma, chronic obstructive pulmonary disease (COPD), respiratory infection, oxidative stress.

INTRODUCTION

In the past few decades, global urbanisation requiring intense energy consumption has resulted in increased emissions into the atmosphere and a decrease in urban air quality. As a consequence, hundreds of millions of individuals experience an increased quantity, but also a more diverse variety of ambient air pollution. The air pollutants of most concern include ozone (O_3), nitrogen dioxide (NO_2), and particulate matter (PM). Ozone is a major constituent of photochemical smog and is generated at ground level by atmospheric reactions of NO_2, hydrocarbons, and ultraviolet light. The major source of NO_2 and PM is fossil fuel combustion, primarily from motor vehicles, in addition to energy generation and industry; while in many parts of the developing world, exposure to household biomass combustion for cooking and heating is the major source.[1] The Global Burden of Disease Study[2] reported that PM exposure was the fourth biggest threat to the health of the Chinese population with 1.2 million people dying prematurely in 2010.

Of these common urban air pollutants, PM has been studied in the greatest detail, but there is increasing awareness of independent and direct health effects of NO_2. PM is a general term that refers to a complex mixture of solids or liquids that vary in number, size, shape, surface area, chemical composition, solubility, and origin.[3] The main components of PM, originating from road transport, are engine emissions, brake and tyre wear, and dust from road surfaces. The largest single source of airborne PM from motor vehicles is derived from diesel exhausts, and this is an increasingly important problem in Europe.[4] Owing to the growth in the number of new cars with diesel engines, diesel exhaust particles (DEPs) account for the most airborne PM in most European cities. Biomass combustion particles have a range of physiochemical properties, depending on the nature of the biomass and combustion conditions which, in turn, influences PM toxicity.

The inhalation of toxic particles and gases targets the natural defences of the lung by increasing epithelial permeability, decreasing mucociliary clearance, and depressing macrophage function. Although individual air pollutants will exert specific toxic effects on the healthy or diseased respiratory system, a common chain of molecular events ensue. Human, animal, and *in vitro* experimental studies have demonstrated an increased recruitment and activation of inflammatory cells, and the generation of an array of inflammatory mediators, as well as the activation of intracellular oxidative stress via the generation of free radicals and depletion of protective small molecular weight antioxidants,[5] and antioxidant enzymes.[6] Oxidative stress, in turn, promotes further inflammation via regulation of redox-sensitive transcription factors and signalling via the mitogen-activated protein kinase pathway. DEPs and O_3 are able to increase the production of the allergic antibody immunoglobulin E (IgE), thereby increasing sensitisation to allergens.[7,8] With widespread urban air quality problems across Europe, it is perhaps not that surprising, therefore, that we are experiencing an increased incidence of airway disease, which in turn provides continued momentum to the extensive research effort in this area.

RESPIRATORY SYMPTOMS AND LUNG FUNCTION

In children, epidemiological studies have demonstrated a strong association between exposure to particulate air pollution and cough and wheeze;[9,10] improvement in air quality in Switzerland was found to result in fewer cases of chronic cough in children,[11] as well as cough, wheezing, and breathlessness in adults.[12] Exposure to O_3 at concentrations found in ambient air is associated with a reduction in lung function and induction of respiratory symptoms including cough, shortness of breath, and pain in deep inspiration.[13-17] Human toxicological studies suggest that effects diminish with increasing age, emphasising the importance of ventilation rate, and confirming the intrinsic differences in responsiveness to O_3 among individuals.[13,18,19] NO_2 concentrations have also been associated with cough, wheeze, and shortness of breath in children. Residential traffic-related air pollution exposure, associated with reduced expiratory flows in school children[20] and children relocating to areas of differing air pollution levels, have been reported to experience changes in lung function that mirrored changes in PM exposure.[21] The Southern Californian Children's Health Study (CHS)[22] was first to indicate that urban air pollution has lasting adverse effects on lung development in children, an important finding that is now supported by work from UK (Manchester)[23] and Japan.[24]

Asthma

The role of air pollution in the development of asthma has long been unclear. Recent studies, with a focus on urban areas, however, have begun to report consistent associations. Three European birth cohort studies have reported a positive relationship between traffic-related pollution and doctor-diagnosed asthma.[25-27] The CHS has reported that traffic-related pollutants can cause asthma in children,[22,28] as has a Dutch study in which traffic-related pollution levels at the birth address and incidence of asthma were considered during the first 8 years of life.[29] Not all studies, however, show such a relationship,[30] and such inconsistencies may be due to incomplete exposure assessment or insufficient study power as only a small number of children are likely to be particularly susceptible to the effects of air pollution. Host characteristics that have been implicated to influence the effects of air pollution on asthma include nutritional status, atopy, and social stress.[31-37]

The observation that social stress and traffic-related air pollution are often spatially correlated has prompted research into possible synergies between these two environments. Chronic stress has been

found to modify the risk of asthma associated with traffic-related air pollution exposure;[34] however, findings are not consistent.[35-37] Personal exposures of pregnant women to polycyclic aromatic hydrocarbons (PAHs) have been associated with increased respiratory symptoms,[38] such as asthma, wheeze, cough, and ear infections,[39] among their children over the first year of life. The first trimester (i.e. PM up to 10 micrometres in size [PM_{10}]) and second trimester (NO_2 exposures) were associated with lower lung function parameters in asthmatic children at an age of 6-11 years.[40] These epidemiologic observations are supported by mechanistic findings in mice. Prenatal exposures to PM or DEPs result in higher IgE levels, skewed T helper 2 cytokine responses, impaired lung growth, greater airway hyperresponsiveness, and increased infiltration of inflammatory cells.[41-43] Exposure of pregnant dams to PM has also been found to increase O_3-induced airway hyperresponsiveness, pulmonary cytokines, and epithelial mucous metaplasia in O_3-exposed pups,[44] whilst prenatal exposure to *Aspergillus fumigatus* allergen and/or DEPs appears to result in protection from developing systemic and airway allergic immune responses in the adult offspring.[45] These various observations fit with the report of immature antioxidant defences in the foetus.[46]

Clear strong linkages have been established between air pollution and exacerbation of asthma. Moreover, epidemiological studies point to several potential causal agents for the observed association. Ozone exposure has been linked with hospital admissions,[47,48] worsening of symptoms and rescue medication,[49] as well as asthma attacks, respiratory infections, and reductions in peak flow rate.[50] NO_2 exposure has been associated with emergency room visits, wheezing, and medication use amongst children with asthma,[51,52] whilst controlled-exposure studies of asthmatic volunteers have found that NO_2 can enhance the allergic response to inhaled allergens.[53,54] Evidence of adverse effects of particulate pollution include a negative effect on respiratory function[55] and associations with increased symptoms or hospitalisation.[56] A current key area of research is a focus on the specific relationship between asthma and traffic-related pollutants in urban areas.[57] A recent advance in assessing the effects of air pollution on asthma is the use of biomarkers of airway inflammation and oxidative stress as outcome measures in epidemiological studies.[58,59] Parameters such as distance to a major road or land-use regression models to predict concentrations of traffic-related pollutants among unmonitored individuals are also important developments in air pollution epidemiology.

The important contribution of traffic emissions to urban air pollution has led investigators to examine the relative toxicity of traffic-related PM pollutants. High previous-day concentrations of ambient air zinc have been associated with risks of paediatric asthma exacerbations,[60] while a positive association between ambient concentrations of vanadium, elemental carbon or nickel $PM_{2.5}$ content, and respiratory symptoms or hospitalisations has been reported.[61,62] The effect of size distribution and total number concentration of ultrafine and accumulation mode particles on respiratory hospital admissions in asthmatic children has also been considered.[63] For paediatric asthma, accumulation mode particles and NO_x are relevant, whereas PM_{10} appeared to have little effect.

Polymorphisms in genes involved in antioxidant pathways, airway inflammation, and innate immunity may modify an individual's response to air pollution. Polymorphisms in glutathione S-transferases (*GSTM1* and *GSTP1*) that facilitate the elimination of reactive oxygen species have been associated with breathing difficulties and respiratory symptoms in asthmatic children following increases in ambient O_3 concentrations[64] and an altered response to combined exposures to ragweed pollen and DEPs.[65] *GSTP1* polymorphisms have also been associated with a greater risk of asthma[66] and sensitisation to allergen in association with traffic-related NO_x during the first year of life.[67] In a study in Mexico City, *GSTM1* polymorphisms have been shown to predict asthmatic patients who will benefit from antioxidant supplementation.[65] Polymorphisms in the inflammatory gene for tumour necrosis factor-α and transforming growth factor β may influence lung function to ozone exposure[68] and risk of asthma in children living within 500 m of a major road,[69] respectively. With respect to innate immunity, the absence of measurable CD4 expression on circulating neutrophils in asthmatic children correlated with reduced lung function in the presence of ambient PM.[70]

Chronic Obstructive Pulmonary Disease (COPD)

Large-scale prospective studies used to examine the relationship between air pollution and the development of COPD have provided conflicting outcomes. Whilst the European Community and Respiratory Health Survey[71] did not find a

significant association between urban background air pollution and changes in forced expiratory volume in 1 second (FEV_1) and forced vital capacity, the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults[72] did - reporting a significant negative association between decreased PM_{10} and the rate of age-related decline in FEV_1. A 7 μg/m³ increase in exposure to ambient PM_{10} over 5 years resulted in a more rapid decline in pulmonary function, a high-risk ratio to develop COPD, and poorer respiratory health in women living near high traffic areas or industrial sources.[73] One possible reason for these differing findings is the possible influence of early life exposures on COPD development.[74] It is clear that PM exposure both impairs normal lung function growth in children[22] and accelerates the natural decline in adult lung function.[75] It has been hypothesised that, in turn, a reduced lung function growth impairs the innate immunity of the lung and increases vulnerability to infection, possibly as a consequence of increased nasopharyngeal carriage.[76,77] In support of the latter, there is evidence from both the developing and developed world that exposure to PM increases susceptibility to bacterial infection in children.[78,79] Epidemiological evidence is also accumulating that infants subjected to higher prenatal levels of air pollution may be at greater risk of developing respiratory conditions. A birth cohort study found that prenatal ambient PAHs and $PM_{2.5}$ exposures led to neonates having a reduction in T cells and a concomitant increase in B lymphocytes and changes in cord serum IgE levels.[80]

COPD patients exposed to increased PM concentrations experience a worsening of symptoms and higher morbidity as assessed by emergency room visits or hospital admissions.[81-84] Worsening of the condition has also been demonstrated in several panel studies, reporting decreases in pulmonary function,[81] heightened night-time chest symptoms,[85] and increased rescue bronchodilator use.[86] Dominici and workers[83] reported almost a doubling of admissions for COPD exacerbations for every 10 μgm³ of increase in $PM_{2.5}$. Overall, epidemiological evidence also indicates an elevated mortality rate among individuals with COPD following exposure to PM,[87-89] although data collected from the American Cancer Society as part of the Cancer Prevention Study[90] were unable to detect such an association. It has also been observed that an effect of PM on mortality amongst COPD patients may be more pronounced among individuals with a lower income and socioeconomic status.[91] In addition to the well cited detrimental effects of PM, both O_3 and NO_2 have also been associated with increased hospital admissions[75] and respiratory mortality in patients with COPD.[92] Polymorphisms in the antioxidant gene coding for glutamate-cysteine ligase as well as *GSTM1* and *GSTP1* correlate with the risk of COPD.[93-95]

Respiratory Infection

Numerous epidemiological and experimental studies indicate an association between exposure to the common air pollutants and combustion products of biomass fuels, and an increased risk for viral respiratory infections.[96] Positive observations have been found between pollutant exposures and rates of chronic cough and bronchitis[97] in addition to admissions for pneumonia and influenza.[98,99] Acute increases in PM concentrations have been shown to significantly increase hospital admissions for respiratory infections.[83,100] There is also epidemiological evidence linking indoor exposure to air pollutants from the combustion of biomass fuels to pneumococcal infection.[101] A meta-analysis of studies in the developing world estimated that the odds ratio for severe pneumonia in children exposed to biomass smoke and other high PM-emitting fuels is 1.78 (95% CI, 1.45–2.18).[79] Furthermore, associations between exposure to biomass combustion and death due to respiratory infections in children have been reported,[102-104] as well as observations suggesting that NO_2 could enhance the severity of viral-induced asthma.[105]

Experimental studies in humans, animals, and *in vitro* reinforces the epidemiological evidence that air pollution can significantly affect susceptibility to and morbidity from respiratory infection. NO_2 has been shown to increase the morbidity of Sendai virus in mice,[106] whilst synergism between NO_2 (and O_3) and rhinovirus infection in human basal and bronchial epithelial cells have been found.[107] Carbon black and concentrated ambient particles have been shown to augment respiratory syncytial virus infection in mice,[108] reduce the capacity of macrophages to phagocytise this virus,[109] and reduce *Streptococcus pneumoniae* clearance from the lungs of mice.[110] Numerous studies of DEPs have reported increased susceptibility and response to influenza infection in mice and in human respiratory epithelium.[111-113]

Several potential mechanisms exist that may be involved in an environmental pollutant-induced

alteration of host immunity. Oxidative stress, particularly within the protective epithelial lining fluid of the lung,[113,114] is supported by observations of a protective effect of antioxidants to DEP-induced enhancement of influenza infections.[112] Alternatively, air pollutants may modulate the antiviral defences by reducing the ability of macrophages to phagocytise viruses.[109] Other important components of innate immunity which have been shown to be a target for air pollutants are the surfactant proteins SP-A and SP-D[115] and epithelial cell tight junctions.[116]

LOOKING FORWARD

Modern urban air pollution is a serious public health hazard. Furthermore, as adverse effects on the respiratory system have been observed at concentrations below ambient air quality standards, it appears that current legislation should be more stringent, and that pollution control strategies should focus on specific sources and constituents deemed to be most damaging. Specific areas of research that will prove invaluable if the effects of air pollution on airway disease are to be reduced, include identifying the most predictive exposure methods as well as suitable clinical markers (for both pollutant exposure and oxidative stress) to gain a more accurate assessment of the effectiveness of air quality policies. Further work in identifying susceptible populations is also required. For example, increasing our knowledge of genotype-phenotype associations and inheritable gene-environment interactions involved in the host response to environmental air pollutants will be particularly important. Another, more specific, research direction that requires both epidemiological and mechanistic studies is the way in which air pollutants influence respiratory infections, again especially in particularly vulnerable subgroups of the population.

Success in identifying susceptible subpopulations will be necessary if diagnostic screening and therapies/preventive agents for pollution-induced respiratory diseases are to be developed. Individualised pharmacotherapy with antioxidant (by reducing oxidative stress and/or enhancing antioxidant defences of the human airway) and anti-inflammatory agents, to stem the damaging effects of air pollutants in vulnerable subgroups, may well prove to be an option in our increasingly urbanised world. In addition to focused, high quality research, a cleaner and healthier environment ultimately relies upon collaborative efforts of the government (through legislation and education) and the public (through, for example, responsible use of transportation), and effective translation of the scientific evidence base into risk communication and public policy.

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