

Link between environmental air pollution and allergic asthma: East meets West

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Abstract: With the levels of outdoor air pollution from industrial and motor vehicle emissions rising rapidly in the fastly-industrializing countries of South East Asia, the prevalence of asthma and allergic diseases has also been increasing to match those in the West. Epidemiological and experimental exposure studies indicate a harmful impact of outdoor air pollution from vehicles and factories both on the development of allergic diseases and asthma and the increase in asthma symptoms and exacerbations. The level of outdoor pollution in Asia is much higher and more diverse than those encountered in Western countries. This may increase the impact of outdoor pollution on health, particularly lung health in Asia. This review discusses the constituents of air pollution in Asia with a special focus on studies in mainland China and Taiwan where the levels of pollution have reached high levels and where such high levels particularly in winter can cause a thick haze that reduces visibility. The onus remains on regulatory and public health authorities to curb the sources of pollution so that the health effects on the population particularly those with lung and cardiovascular diseases and with increased susceptibility can be mitigated.

Keywords: Allergy; environmental air pollution; particulate matter (PM); ozone (O₃); nitrogen dioxide (NO₂); asthma

Submitted Sep 09, 2014. Accepted for publication Dec 03, 2014.

doi: 10.3978/j.issn.2072-1439.2014.12.07

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2014.12.07>

Introduction

There is increasing evidence of the negative health impact resulting from environmental air pollution, in particular that associated with respiratory diseases and allergy. The increasing prevalence of respiratory diseases and allergy such as asthma has drawn attention to the potential role of air pollution in causing this. While this has been first noticed and reported in Europe and North America, this is now being seen in many of the rapidly-growing economies of South East-Asia, particularly in China as a result of the fast pace of urbanization and increased energy consumption that occurs with rapid industrialization and the increasing number of vehicles (1). This is having a significant impact on mortality and health of Asian populations and air pollution is one of the major factors that affects the health

of Asians (2). Recent data published by the *Health Effects Institute* indicate that a 10 µg/m³ increase in PM₁₀, the coarse particulate fraction of air pollution, is associated with an increase in mortality of 0.6% in daily all natural cause mortality in major cities in India and China (3). The health effects of air pollution particularly on the common lung diseases such as asthma and COPD are also being felt particularly in Asia. The low levels of allergy and asthma that have been seen previously is now rising to match those levels observed in Western countries, and both epidemiological cohort and experimental exposure studies provide evidence to implicate a harmful impact of traffic air pollution on both the development of allergic diseases and asthma and the increase in asthma symptoms and exacerbations. Experimental exposure studies also indicate

a causative relationship between air pollution and allergic airways disorders through the induction of inflammation and oxidative stress in the lungs leading to a preferential T-helper type 2 lineage. In this review, we will examine this evidence implicating the deleterious effect of environmental pollution. One of the major issues of interest will be whether the much higher levels of environmental pollution in Asia will lead to a greater impact on lung diseases particularly asthma and allergic diseases.

Sources and constituents of outdoor pollutants

Outdoor pollutants come from many potential sources, including the combustion of fossil-fuels in power stations and factories, and from car engine, and also from natural sources, e.g., desert sand. According to their source, chemical composition, size, and mode of release into outdoor environments, air pollutants can be classified as primary and secondary, and as gaseous and particulate pollutants. Pollutants that are directly emitted into the atmosphere are primary pollutants such as sulphur dioxide (SO_2), some nitrogen oxide (NO_x) air pollutants, consisting of nitric oxide (NO) and nitrogen dioxide (NO_2), carbon monoxide and particulate matter (PM) while secondary pollutants that form in the air as a result of chemical reactions with other pollutants and gases include ozone (O_3), NO_x , and some particulates. PM is a mixture of particles varying in number, size, shape and chemical composition and produced particularly by diesel-powered motor vehicles but can also be produced from diverse sources, such as factories, power generation, wood burning and biomass fuel, on construction sites, and from mining areas. Other constituents of PM include transition metals, polycyclic aromatic hydrocarbons, and environmentally persistent free radicals. Also usually, traffic-associated PM is mixed with other non-combustion sources such as tyre elements, dust from road and brake lining components. Diesel exhaust particles (DEP) are the particulate component of diesel exhaust, which includes diesel soot and aerosols such as ash particles, metallic abrasion particles, sulphates and silicates.

The size of PM is dependent on its source either natural or anthropogenic or whether it is derived from combustion or not. PM is categorized on the basis of its aerodynamic diameter. PM consists of particles of various sizes define as coarse PM (2.5–10 μm ; PM_{10}), fine PM (0.1–2.5 μm ; $\text{PM}_{2.5}$); or ultrafine PM (<0.1 μm ; $\text{PM}_{0.1}$), putting the ultrafine into the nanosize range. PM particularly of the fine and ultrafine categories can be inhaled directly deep into the lungs and

can reach the small airways and alveoli, with potential interactions with alveolar epithelial cells and alveolar macrophages. In addition, ultrafine particles in the nano-sized range can penetrate through the alveolar epithelial-endothelial layer and get into the blood stream and thus may adversely affect different body organs (4). Alternatively, the inflammation induced by air pollution in the lungs may spill-over into the circulation to affect other organs.

Although it is usual and simple to consider the effect of air pollution in terms of each of these components, it is important to note that the mix of pollutants may be more toxic than its constituent parts. In addition, components of pollution are different from site to site, even within the same neighbourhood, and these may lead to different types or degrees of effects. The constituents of pollution are also dependent on the different sources and on climatic factors.

Effects of O_3

Interactions between NO_x and hydrocarbons released from traffic and/or industrial sources catalyzed by photochemical reactions lead to the formation of O_3 which is a major component of vehicle-based pollution particularly on hot summer days. Exposure of human airway epithelial cells to O_3 (100 ppb) caused the release of proinflammatory cytokines such as GM-CSF and sICAM-1, which was higher in cells from asthmatic patients compared to non-asthmatic patients (5). In studies in rodents, one acute exposure to O_3 induced an airway neutrophilia with bronchial hyperresponsiveness associated with an increase in airway smooth muscle contractility that is p38-MAP kinase dependent (6), while chronic exposure leads to emphysema (7). Under high levels of O_3 exposure (0.4 ppm for 2 hours), there is a reduction in FEV_1 and an increase in bronchial responsiveness which was greater in asthmatics compared to non-asthmatic individuals, although the symptoms were similar (8). Horstman found that asthmatics with the lowest FEV_1 had a greater fall in FEV_1 on exposure to O_3 (9). On the other hand, Nightingale *et al.* showed that in both normal and asthmatic subjects, there was an equivalent fall in FEV_1 on exposure to 200 ppb O_3 for 4 hours, with increased neutrophils in induced sputum with no increase in eosinophilic inflammation (10). Halonen *et al.* [2008] reported a positive association between O_3 and admissions for asthma and COPD in the elderly and between O_3 levels and asthma emergency visits in children (11). They also documented increased hospital admissions (or emergency department visits) of respiratory disease patients (e.g., asthma) after exposure to O_3 levels

of 110 ppb in ambient air. Jörres *et al.* [1996] found that bronchial allergen responsiveness increased in mild allergic asthmatic subjects after O₃ exposure (0.25 ppm) for 3 hours (12). Likewise, Peden *et al.* [1995] reported enhanced nasal inflammatory responses to local allergen challenge after O₃ exposure in subjects with perennial allergic rhinitis (13). Short-term changes in O₃ levels have been associated with increased mortality in a study of 95 urban communities such that a 10 ppb increase in O₃ levels has been associated with a 0.52% increase in daily mortality even after taking into account the influence of PM (14). Therefore, O₃ remains an important constituent of environmental pollution, capable of worsening asthma.

Effects of NO₂

NO₂ which is a component of photochemical pollution is emitted from car exhaust, power plants, and burning of fossil fuels. NO₂ exposure causes chronic and acute changes in lung function, bronchial neutrophilic inflammation, and proinflammatory cytokine production. Previous exposure to NO₂ can increase the response to allergen challenge in atopic asthmatics (15-17). In children, exposure to NO₂ increased the likelihood of wheeze, shortness of breath, and chest tightness; each 20-ppb increase in NO₂ increased both likelihood of any wheeze or chest tightness, and days of wheeze or chest tightness (18). Bevelander *et al.* [2007] reported in a mouse model of allergen sensitisation that one hour of exposure to 10 parts per million NO₂ increased bronchoalveolar lavage fluid levels of total protein, lactate dehydrogenase activity, and heat shock protein 70, and promoted the activation of the pro-inflammatory transcription factor, NF-κB, by airway epithelial cells. This effect was dependent on the presence of the innate immune TLR4 and MyD-88 (19). However, in a clinical review, Hesterberg *et al.* [2009] concluded that NO₂ induced lung inflammation reported in human clinical results do not establish a mechanistic pathway leading to adverse health impacts for short-term NO₂ exposures at levels typical of maximum 1-h concentrations in the present-day ambient environment (i.e., below 0.2 ppm) (20). However, the overall view is that NO₂ has the potential of worsening asthma symptoms and cause adverse effects on lung function and airway responsiveness.

Effects of PM

Experimental exposure to PM can induce oxidative stress,

airway hyper-responsiveness, and airway remodeling on its own or in combination with allergic sensitization (21,22). Control exposure of normal volunteers to reconstituted 200 µg/m³ of DEP in a chamber caused neutrophilic inflammation and neutrophil activation (23). In a study of asthmatic patients walking on a London polluted street for 2 hours, the reduction on FEV₁ and the degree of neutrophilic lung inflammation observed after the walk was associated most consistently with exposures to ultrafine particles and elemental carbon (24).

In asthmatic children and adults, a short-term exposure to fine and ultrafine particles has been associated with asthma symptoms, particularly in allergic children, in two studies from California (25,26). There is also evidence that long-term exposure to PM is associated with poorly controlled asthma and reductions in lung function in children and adults (27,28). Short-term and long-term exposure to PM_{2.5} or PM₁₀ have also been associated with increased health-care use associated with exacerbations and poorly-controlled asthma, even after the potential contributions of other pollutants have been taken into account in European, US studies (29-32). One study from Korea reported also that short-term exposure to PM₁₀ and NO₂ was associated with a risk of hospital admission for asthma (33). However, in studies reported from China (Shanghai, Guangzhou, and Lanzhou), the contribution of PM in increasing the risk of hospitalization for asthma or other respiratory condition was of lesser extent, with the gas components (SO₂ or NO₂ or both) being more important factors (34-36).

In summary, substantial evidence supports the idea that ambient levels of PM exacerbate existing asthma, particularly by contributing to oxidative stress and allergic inflammation, and some evidence exists in support of PM as a cause of new cases of asthma.

Studies of PM in China

Studies of air pollution in China have focused on the analysis of important chemical constituents of PM_{2.5}. A recent study compared PM_{2.5} collected from urban versus suburban areas of Beijing and from a positive matrix factorization identified the PM_{2.5} to be coming from seven sources: secondary sulphate/nitrate (30%), coal combustion (22%), traffic emissions (12%), dust/soil (12%), secondary organic aerosol (10%) and industry (7%). In urban areas, there was a greater contribution from traffic emissions, combustion and secondary organic aerosol.

More importantly, the potential health effects of $PM_{2.5}$ on inflammatory biomarkers was related to the secondary sulphate/nitrate and dust/soil and pulmonary function deterioration to dust/soil and industry (37). Another study in Beijing examined the role of these particles and associated chemicals in causing mortality and morbidity and found that the short-term effects of $PM_{2.5}$, sulphates, and NO_3 were worse in the winter months and that traffic sources and re-suspended road dust were particularly important contributors to ill-health in Beijing (38).

On the other hand, another feature that appears specific to the current state of pollution in China is the increased frequency of the haze periods which are periods of severe reduction in visibility due to light extinction caused by PMs. These episodes have become more frequent in the city clusters of the Yangtze Delta River, Beijing-Tianjin area, and the Pearl River Delta region. Haze usually occurs on very severe polluted days with very high particle levels with relatively high humidity, with the PM containing high levels of water soluble ammonium sulphate and/or nitrate that leads to visibility impairment. In addition, there is an increase in water soluble trace elements such as copper, vanadium and zinc during haze days concentrating particularly in the 0.5 to 1.0 μm size particles reported in Beijing and the levels of these elements closely correlating with plasmid DNA damage rates (39). There is already evidence from Guangzhou that these haze periods, which by definition occur on 278 days per year, caused greater mortality than non-haze periods, particularly due to cardiovascular and respiratory causes (40), and is associated with the largest risk of hospital admissions for all conditions (35).

Another potential effect of the haze in China is the possibility that the high concentrations of $PM_{2.5}$ during a haze period can carry bacteria and viruses directly into the lungs, explaining the high levels of respiratory infections that are admitted to hospital during that time. In addition, there has been suggestion that the increasing cases of infection with avian influenza AH7N9 virus during January 2014 could have been related to the haze of the 2013 winter in China (41). Using metagenomic assays with sufficient sequencing depth, airborne microbes including bacteria, archaea, fungi, and dsDNA viruses have been identified at the species level in $PM_{2.5}$ and PM_{10} collected during a haze period in January 2013 in Beijing. Although the majority of the inhalable microorganisms were soil-associated and nonpathogenic to humans, this finding supports the possibility of PM carrying bacteria (and possibly viruses)

deep into the lungs.

The impact of environmental pollution on lung health in China has been well illustrated by the studies that have contrasted the changes that were noted around the Beijing Olympics in 2008 when there was a transient reduction in air pollution levels caused by closure of factories and a reduction in vehicles in circulation. Closing factories that produced construction materials led to a reduction in SO_2 emissions for the sector by 85%, while levels of NO_x and non-methane volatile compounds were reduced by 50% from mobile sources including vehicles. Prohibition of building construction reduced PM_{10} emissions by 90% and total PM_{10} by 35%. There were reductions in the mean concentration of carbon monoxide (-48%), NO_2 (-43%), elemental carbon (-36%), $PM_{2.5}$ (-27%), organic carbon (-22%), and sulfate (-13%) from the pre-Olympic to the during-Olympic period, but O_3 concentrations increased (24%). Pollutant concentrations increased substantially from the during- to post-Olympic period for all the pollutants except for O_3 and sulfate (42). From the pre- to during the Olympic Games period, there were significant decreases in levels of H^+ , exhaled NO , nitrate and nitrate and 8-isoprostanes measured in exhaled breath condensates and urinary 8-OH-deoxyguanosine, with an increase from/during to post Olympic phase in young fit normal Beijing residents (43), indicating a reduction in oxidative stress burden. In addition, in asthmatic subjects, there a rapid reduction in exhaled NO in children associated with the reduction in pollution, a marker of airway inflammation (44). This reduction in pollution also has beneficial effects on asthma with a significant reduction in asthma visit to outpatients of a central Beijing Hospital (45).

Air pollution, allergic rhinitis and asthma in mainland China

The role of pollution in the prevalence and exacerbations of allergic diseases in Asia has been previously reviewed (46). Overall there is good evidence to support the notion that there has been an increase in allergic rhinitis in China, similar to the increase observed in all western countries. In Chinese school children aged 13-14 years, the prevalence of physician-diagnosed allergic rhinitis increased from 17.4% in 1994-1995 to 22.7% in 2001 (47).

In a carefully done study in Beijing in 2009-2010, the daily number of outpatient visits for allergic rhinitis was associated with increasing concentrations of SO_2 and also of PM_{10} and NO_2 (48). Besides, all the three air pollutants

(PM₁₀, SO₂ and NO₂) were associated with increased possibility of hospital visits for every 10 µg/m³ increase of pollutant concentration. In a cross-sectional questionnaire study in 11 large cities in China, there was a correlation between the adjusted self-reported prevalence of AR with the concentration of SO₂, but not with NO₂ and PM₁₀ or with meteorological factors such as average temperature, relative humidity, hours of sunshine and precipitation (49).

In general, there has been an association with respiratory symptoms with increasing pollution. For example in a questionnaire survey of 6,730 Chinese children attending kindergarden in seven cities in Northeast China, the prevalence of respiratory symptoms was higher among children living near a busy road, those living near chimneys or a factory, those having a coal-burning device, those living with smokers, and those living in a home that had been recently renovated. Among girls, PM₁₀ was associated with persistent cough, persistent phlegm, and wheezing. NO₂ concentration was associated with increased prevalence of allergic rhinitis among girls (50). In a study of elementary school zones in four Korean cities, there was a significant increase in the risks based on the odds ratios of treatment experiences for allergy-related diseases such as asthma and allergic rhinitis in the school group with traffic-related pollutants and the school group with complex pollutants (2.12 and 1.59, respectively), in comparison to the school groups with no exposure to pollutants (51).

The generally low prevalence of asthma in China is now on the increase, just as allergic rhinitis (52). Exposure to air pollutants particularly particulates and gases is related to increasing prevalence of respiratory symptoms such as persistent cough, sputum production, and current asthma symptoms in children (53) and to hospital admissions for asthma with a higher risk in children (54). In Asian populations, there is an increased prevalence of asthma and asthma-like symptoms in association with exposures to air pollution, which supports pollution as a cause of increasing asthma prevalence (3).

Studies of air pollution and allergic diseases in Taiwan

Historically, relying upon the archived air quality data, accumulated evidence from the study of various populations in Taiwan supports the link between ambient air pollution and allergic diseases. In Taiwan, Environmental Protection Agency (EPA) (<http://taqm.epa.gov.tw>) has long established air quality monitoring stations across different regions of Taiwan, including those for real-time monitoring of

ambient air, traffic and industrial pollutants

Epidemiological studies investigating the impact of air pollution on allergic diseases and respiratory health has been documented. In a cross-sectional study (55) of 32,143 Taiwanese school children with a parent-administered questionnaire, the prevalence of allergic rhinitis was shown to be significantly associated with pollutant gases, SO₂, CO and NO_x, with adjusted odds ratio ranging from 1.05 to 1.43 per 10 ppb change for SO₂, NO_x and O₃, 100 ppb change for CO, and 10 µg/m³ change for PM₁₀. Similarly, in a study (56) of 5,072 primary school students in six urban, rural and petrochemical industrial communities, respiratory health was assessed by evaluation of the children's respiratory symptoms and diseases using a parent-completed questionnaire. The results showed that the school children in the urban communities had significantly more respiratory symptoms, including chronic cough, shortness of breath, and nasal symptoms, and diseases (sinusitis, wheezing or asthma, allergic rhinitis, and bronchitis) when compared with those living in the rural community. However, only nasal symptoms of children living in the petrochemical communities were more prevalent than those living in the rural community. Further, in a survey study (57) of the prevalence for physician-diagnosed asthma in 331,686 middle-school students in Taiwan, it was shown that asthma prevalence rates were associated with non-summer (June-August) temperature, winter (January-March) humidity, and traffic-related air pollution, especially CO and NO_x, for both girls and boys after adjusting for age, history of atopic eczema and parental education.

To evaluate the time trend and the relationship between air pollution and hospital visits for asthma in Taiwan from 2000 through 2009, it was shown that relative to the respective lowest exposure quartile of air pollutants, the adjusted relative risks of the outpatient visits in the highest quartile were significant for four criteria pollutants (SO₂, NO_x, CO, and PM₁₀) in the children (aged 0-18), adult (aged 19-64) and elderly (aged ≥65) study populations, while for inpatient visits, a positive association with CO levels in the children population was noted (58). As a corollary, the rate of daily clinic visits was found to be associated with all four criteria air pollutants, while people over 65 years of age were found to be the most susceptible population, and the estimated pollution effects decreased as the exposure time lag increased (59). This study also suggested that the population density within a given community and the seasonal variation in air pollution levels may modify the effects of air pollution. The observation that higher levels

of ambient air pollutants increased the risk of hospital admissions for asthma was further substantiated from the studies of hospital admissions for asthma in two major cities of Taiwan during the period from 1996 through 2003 (60,61). Moreover, to evaluate the relationship between air pollution and asthma exacerbation in children and adults, Sun *et al.* (62) found significant correlation between the levels of NO₂ ($r=0.72$), CO ($r=0.65$) and PM₁₀ ($r=0.63$) and ER visits for asthma in children, but not in adults.

Recently, Wang *et al.* (63) investigated the associations between daily outpatient visits and air pollution during the period 2007–2011 in a heavily industrial area in northern Taiwan. The results showed that ambient air temperature and relative humidity appeared to be negatively associated with respiratory diseases. In this study, NO and NO₂ were found to be the prominent air pollutants showing positive association with respiratory diseases, while PM₁₀, PM_{2.5}, O₃, CO, and SO₂ showed weaker, but still significant, evidence of association. Importantly, this study also indicated that the newborn, infant and young children (0–15 years) populations are most susceptible to the changing air pollution and meteorological factors. Interestingly, this study also revealed a likely gender difference in susceptibility to the air pollution's effect, where female outpatients appeared to be more sensitive to the changes in air pollution and meteorological factors than their male counterparts.

Furthermore, in a study integrating spatial and temporal approaches, children (aged 0–15 years) were shown to have the highest number of total asthma visits (64). Seasonal changes in the levels of PM₁₀, NO₂, O₃ and SO₂ were also evident. Among the four pollutants studied, the elevation of NO₂ concentration had the highest impact on asthma outpatient visits on the day that a 10% increase of concentration caused the asthma outpatient visit rate to increase by 0.30% (95% CI: 0.16–0.45%). For ER visits, the elevation of PM₁₀ concentration, which occurred 2 days before the visits, had the most significant influence with an increase of 0.14% (95% CI: 0.01–0.28%), suggesting that NO₂ and PM₁₀ might have a positive impact on outpatient and emergency settings, respectively. It is worth noting that in a study evaluating the influence of meteorological parameters on the distribution of the five criteria air pollutants (SO₂, CO, O₃, PM₁₀ and NO₂, collectively calculated as daily air pollution index) in northern Taiwan from 1995 to 2001, Yu *et al.* (65) presented evidence that three types of weather patterns (high-pressure recirculation, prefrontal warm sector and the southwesterly wind system)

impacted the severity of air pollution, with the wind speed and mixing height of less than 2.1 m/s and 360 m, respectively, as being the most influential parameters in enhancing the impact of air pollution. In this study, it was also pointed out that the correlation coefficients for air pollutants and three meteorological parameters (wind speed, mixing height and ventilation index) were low, suggesting the likely mobile sources being the dominant factors affecting ambient air quality in northern Taiwan.

Conclusions

There is now sufficient evidence to indicate that the observed detrimental impact of environmental pollution on asthma and allergic disease first observed in the West is now occurring in the East. The evidence in the East also supports the finding that outdoor air pollution poses significant adverse effects on allergic diseases and respiratory health, while its risk level may be modified by the temporospatial and meteorological changes. Children and the elderly are particularly vulnerable to the effects of air pollution. While further extensive and more comprehensive studies are needed, the currently-available data would serve as an important evidence-based foundation in establishing the link between the outdoor air pollution and allergic diseases. It remains uncertain as to whether the more severe levels of air pollution in the East will lead to greater deleterious effects. This is the reason why the health implications and importance of regional and intra-city differences and combination of pollutant constituents should continue to be investigated. While the epidemiological evidence alone still carries some degrees of uncertainty in defining the environmental etiology, accumulated experimental evidence has provided evidence supporting their causative role. The solution to this problem is of course to reduce emissions of these pollutants and this reduction is possible as shown during the Beijing Olympic Games. On the other hand, efficacious preventive measures and treatments need to be found.

Acknowledgements

KFC is supported by a British Heart Foundation grant examining the effect of DEPs in London and by NIHR Respiratory Biomedical Research Unit at the Royal Brompton NHS Foundation Trust and Imperial College London. He is also a Senior Investigator of NIHR UK and a Visiting Professor of Guangzhou Medical University,

Guangzhou, China. SKH is supported in part by grants from National Health Research Institutes, Taiwan, NHRI-102A1-PDCO-03010201 and Ministry of Health, Taiwan (EODOH01).

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Zhang Q, Qiu Z, Chung KF, Huang SK. Link between environmental air pollution and allergic asthma: East meets West. *J Thorac Dis* 2015;7(1):14-22. doi: 10.3978/j.issn.2072-1439.2014.12.07