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Air pollution and health: emerging information on susceptible populations

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Abstract

Outdoor air pollution poses risks to human health in communities around the world, and research on populations who are most susceptible continues to reveal new insights. Human susceptibility to adverse health effects from exposure to air pollution can be related to underlying disease; demographic or anthropometric characteristics; genetic profile; race and ethnicity; lifestyle, behaviors, and socioeconomic position; and location of residence or daily activities. In health research, an individual or group may have an enhanced responsiveness to a given, identical level of pollution exposure compared to those who are less susceptible. Or, people in these different groups may experience varying levels of exposure (for example, a theoretically homogeneous population whose members differ only by proximity to a road). Often the information available for health research may relate to both exposure and enhanced response to a given dose of pollution. This paper discusses the general direction of research on susceptibility to air pollution, with a general though not an exclusive focus on particulate matter, with specific examples of research on susceptibility related to cardiovascular disease, diabetes, asthma, and genetic and epigenetic features. We conclude by commenting how emerging knowledge of susceptibility can inform policy for controlling pollution sources and exposures to yield maximal health benefit and discuss two areas of emerging interest: studying air pollution and its connection to perinatal health, as well as land use and urban infrastructure design.

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Keywords

Outdoor air; Particulate matter; Susceptible populations; Genetics; Diabetes

Introduction

> "The moral test of a government is how it treats those who are at the dawn of life, the children; those who are in the twilight of life, the aged; and those who are in the shadow of life, the sick, the needy, and the handicapped."
>
> Hubert Humphrey, 1976

Adverse health effects caused by airborne pollution are restricted primarily to susceptible populations. The actual risk of any one individual is quite small, but because of the large number of exposed people, the overall population risk is significant. Ferreting out which individuals are at greatest risk for adverse events is one of the challenges of air pollution research. This theme was the topic of a special symposium at an international meeting on air pollution research held in March, 2010 (http://aaar.2010specialty.org/), and the material in this article expands upon the remarks we provided at that event.

Individuals respond differently to exposure to air pollution, and features contributing to these variations are generally discussed under the concept of susceptibility. The distribution of potential characteristics that may confer special vulnerability to air pollution exposure, such as altered deposition and clearance of pollutants, underlying disease, age, or genetic polymorphisms, as well as population characteristics including nutrition and socioeconomic status, and their change over time, affect the proportion of susceptible individuals in society. Higher death rates in response to exposure to air pollution are found in individuals already affected by chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), pneumonia, and ischemic cardiac disease.

Scientists from the U.S. Environmental Protection Agency recently discussed the varying definitions of susceptibility and vulnerability used in air pollution research, with a focus on particulate matter (PM) exposure, and proposed an inclusive definition of susceptibility:

> "Individual- and population-level characteristics that increase the risk of PM-related health effects in a population including, but not limited to: genetic background, birth outcomes (e.g., low birth weight, birth defects), race, sex, life stage, lifestyle (e.g., smoking status, nutrition), preexisting disease, SES (e.g., educational attainment, reduced access to health care), and characteristics that may modify exposure to PM (e.g., time spent outdoors)."
>
> (Sacks et al. 2011)

This definition defined the bounds of their review of recent literature on susceptibility to PM-related health effects, which was limited to epidemiological studies providing results from stratified analyses comparing different population groups (older versus younger individuals) and supporting evidence on biological plausibility for susceptibility among these groups from controlled human exposure and toxicological studies. Their review

covered studies on susceptibility by life stage, sex, race–ethnicity, obesity, preexisting diseases, genetics, and socioeconomic status. Our current effort complements their work by focusing on specific areas of air pollution research and including comments from our own research perspectives.

The previously published review of current literature is an excellent synthesis of the state of knowledge on susceptibility to PM and is especially useful for framing how pollution control measures may affect population health as a whole. Evaluating pollution effects on people with a particular disease state (e.g., asthma, diabetes) or of a particular age group is very common in epidemiology. Genetic susceptibility may also be defined at a population level, more often within a specific epidemiologic cohort where approval to identify gene variants that may relate to a person's response to a given environmental exposure has been granted. Race and ethnicity are used as potential markers of susceptibility, especially in countries where recording of these characteristics is routine, such as the USA. Data on lifestyle, behaviors, and socioeconomic indicators, including smoking, dietary habits, occupation, income, and education, are often available through questionnaire data. And location of residence whether in relation to a roadway, pollutant source, defined according to characteristics of the neighborhood in terms of physical features, resources or types and prevalence of individuals living in a particular zone, and/or defined according to some geopolitical feature, from city blocks to nations, can be a way to define populations to evaluate susceptibility.

The array of categories listed above can capture information on a feature of a person or group that makes them more or less responsive to a given, identical level of pollution exposure, or results in a higher or lower level of pollution exposure. These categories also may be related to *both* exposure and susceptibility.

In addition to this complexity, correlations exist among and between the categories used to define susceptibility. Prevalence of diabetes, lack of nutritious food availability, and pollution exposure may all be higher among certain lower income populations. Thus, although a decision to review air pollution susceptibility literature based on stratified epidemiologic analyses is sensible, these correlations make interpretation of studies potentially challenging. Additionally, studies that categorize populations by the social construct of race–ethnicity require careful interpretation (Kaufman and Cooper 2001). The use of ancestry informative markers to identify race/ethnicity from a genetic perspective may be of use in guiding appropriate interpretation.

This paper addresses emerging knowledge in PM susceptibility, focusing on cardiovascular disease, diabetes, asthma, and genetic and epigenetic factors related to susceptibility. Although long-term exposure to air pollution is of great importance for public health, potentially shortening life span and leading to disease onset and progression, our framework of evaluating individuals with preexisting disease or genetic susceptibilities is most relevant to outcomes associated with acute air pollution exposures. Insights derived from this research can be applied to improve population health. The literature cited is intended to illustrate examples rather than provide a comprehensive review. Finally, we discuss future directions for research on susceptibility to air pollution.

Cardiovascular disease

Cardiovascular events in human populations

The World Health Organization (WHO) has estimated that exposure to PM is responsible for more than 800,000 deaths worldwide each year (World Health Organization 2008). This estimate is based on more than 100 epidemiology studies conducted throughout the world demonstrating an association between PM and increased risks of myocardial infarction, arrhythmia, heart failure, stroke, and other adverse health effects. The American Heart Association published a scientific statement in 2004, which was updated in 2010, that concluded that exposure to PM contributes to CV morbidity and mortality (Brook et al. 2010). Although the risk of mortality associated with exposure to PM for an individual is very low, the large pool of susceptible people with CV disease, as well as the ubiquitous nature of air pollutants, is responsible for the large numbers of deaths. Traditional CV risk factors account for the majority of cardiac events and their control has been recognized to be important in preventing CV disease. However, it is well known that CV events are usually triggered by additional factors; PM is increasingly becoming recognized as such a factor, which can trigger CV events in susceptible populations within hours to days after exposure (Tofler and Muller 2006). The risk for mortality associated with PM is also high in people with pulmonary disease, but there is a much larger at risk population with CV disease.

The NMMAPS, a study of 100 cities in the USA, reported a 0.6% (0.3–1.0) increase in cardiopulmonary mortality per 20 $\mu g/m^3$ increase in PM_{10} (Dominici et al. 2003). A study which examined daily mortality in several European cities reported a 1.5% (0.9–2.1) increase in cardiovascular mortality per 20 $\mu g/m^3$ increase in PM_{10} (Analitis et al. 2006). When CV events were broken into categories, a 10-$\mu g/m^3$ increase in PM_{10} was associated with the largest increased hospitalization rates for heart failure, and also for ischemic heart disease, cerebrovascular disease, and heart rhythm (Dominici et al. 2006). However, in an indication that PM also affects vascular events, the Women's Health Initiative reported greater increased risk of stroke and cerebrovascular disease associated with chronically elevated levels of $PM_{2.5}$ than of coronary heart disease or myocardial infarction (Miller et al. 2007). These epidemiology studies provide convincing evidence that the vast majority of mortality is from CV causes and that people with CV disease represent a significant susceptible population.

Pathophysiological responses in human populations

Many controlled exposure and panel studies have reported subclinical pathophysiological changes in individuals exposed to PM. While the responses may not be substantial enough to cause adverse health effects in most populations, even the small PM-induced changes reported in these studies could potentially result in a CV event in a severely compromised individual. Additionally, characterizing these responses can provide an insight into the biological pathways through which PM causes adverse CV events as well as provide biological plausibility to the epidemiology studies.

Systemic inflammation—Several studies have reported associations between PM exposure and systemic inflammation, including changes in acute phase proteins such as C-

reactive protein (CRP) and fibrinogen, pro-inflammatory cytokines, and white blood cells. For example, a recent study reported associations between CRP and interleukin (IL)-6 with PM in subjects with coronary artery disease (Delfino et al. 2008). Associations have also been reported between particle number and IL-6 and particle mass with fibrinogen in a group of myocardial infarction survivors (Ruckerl et al. 2007a). Controlled human exposure studies have demonstrated increased levels of IL-6 and tumor necrosis factor (TNF) after exposure of healthy individuals to diesel exhaust (Tornqvist et al. 2007). Altered numbers of white blood cells were observed in healthy young adults exposed to concentrated ambient air particles (CAPS) (Ghio et al. 2003).

Thrombosis—Increased plasma viscosity and blood fibrinogen concentrations have been associated with short-term changes in PM (French et al. 1997). A marker of platelet activation (sCD40L) has been reported to be increased in association with ultrafine and accumulation mode PM in subjects with coronary artery disease (Ruckerl et al. 2007b). An association was also observed between PM and increased platelet aggregation in healthy individuals (Rudez et al. 2009).

Vascular function—Several recent studies have reported associations between ambient PM levels and vascular endothelial cell dysfunction, as measured by smaller than expected vasodilation following a flow-mediated ischemic event in people with diabetes (O'Neill et al. 2005; Schneider et al. 2008) as well as healthy individuals (Dales et al. 2007). Several studies have also reported associations between ambient PM concentrations and increased arterial blood pressure in healthy adults (Dvonch et al. 2009), those with cardiovascular disease (Ibald-Mulli et al. 2001), and those undergoing cardiac rehab (Zanobetti et al. 2004). Patients with severe heart failure were also observed to have increased pulmonary artery and right ventricular diastolic blood pressure in association with PM (Rich et al. 2008).

Cardiac effects—Many epidemiology and panel studies have shown associations between ambient levels of air pollutants and alterations in heart rate variability (HRV) metrics, which are thought to be markers of imbalance in the autonomic nervous system (ANS). Although findings are not consistent among all the studies, a general pattern is emerging in which associations are found between PM and decreased time domain measurements such as SDNN (thought to reflect overall modulation of the ANS) as well as decreased frequency domain measurements such as HF (thought to reflect parasympathetic activity). These studies are reviewed in the most recent EPA Integrated Science Assessment of PM (U.S. Environmental Protection Agency 2009). Controlled human exposure studies have also observed changes in HRV following exposure of volunteers to PM. For example, healthy elderly volunteers exposed to CAPS experienced a decrease in HRV (Devlin et al. 2003; Gong et al. 2004). Even young healthy volunteers exposed to CAPS experience changes in HRV (Graff et al. 2009; Samet et al. 2009).

Abnormalities in cardiac repolarization are thought to be key factors contributing to the development of arrhythmic conditions which could increase the likelihood of an adverse event. Several recent panel and controlled exposure studies have described associations between PM and altered cardiac repolarization. For example, associations between PM and T wave amplitude were observed in 67 myocardial infarction (MI) survivors (Hampel et al.

2010). The same group also observed changes in deceleration capacity of HR and HRV in patients with ischemic heart disease (Schneider et al. 2010a) and changes in QT duration, T wave amplitude, and T wave complexity in patients with ischemic heart disease (Henneberger et al. 2005). In a controlled exposure study, men with a prior MI experienced exercise-induced ST segment depression during exposure to diesel exhaust (Mills et al. 2007). Even healthy young volunteers experienced increased variance in the duration of the QT interval following exposure to CAPS (Samet et al. 2009).

It should be noted that several studies have failed to find clinical changes similar to those described above. This may be due to the difficulty of consistently measuring the small magnitude changes typically observed even in the positive studies, differences in air pollution mixtures in various locations, differences in populations studied (many of the positive effects were observed in people with cardiovascular disease), or timing of sample collection. Nevertheless, the overall evidence supports the concept that ambient PM is capable of impairing vascular function, increasing thrombotic potential, increasing vascular inflammation, and affecting autonomic nervous system function, especially in high risk populations with cardiovascular disease.

Clearly, people with CV disease experience changes in autonomic nervous system balance, systemic inflammation, increased potential for thrombotic events, and altered vascular function following short-term exposure to PM—but so do healthy age-matched people. Although it could be argued that these changes are more clinically significant in an individual whose CV system is already compromised by disease, an open question is whether the presence of preexisting CV disease makes someone more responsive to PM. Only a handful of studies have attempted to answer this question by directly comparing the response of people with and without CV disease to PM in the same study. These studies suggest that people with CV disease are more responsive to PM than healthy individuals. Park et al. (2005) examined associations between changes in HRV and ambient air pollution in 603 people enrolled in the Harvard Normative Aging Study, of which 29% had ischemic heart disease (IHD) and 67% had hypertension. They found that associations of HRV with $PM_{2.5}$ were stronger in those people with IHD and hypertension than those without these factors. Liao et al. (1999) examined associations between indices of HRV and $PM_{2.5}$ in elderly residents of a retirement center, some of whom had CV disease. Significant associations between HRV and $PM_{2.5}$ levels were only seen in those subjects with CV disease, not those without CV disease.

Effects associated with long-term exposure to PM—In addition to immediate responses to a single exposure (or small number of consecutive exposures), an important question is whether chronic exposure to PM can cause long-term alterations in the CV system, which could lead to progression of CV disease or place a person in a vulnerable state such that acute exposure to a number of stressors (e.g., PM, tobacco smoke, viral infections) could trigger CV events. Residing in locations with higher average PM concentrations has been shown to elevate the risk for cardiovascular mortality and morbidity. A reanalysis of the Harvard Six Cities study showed that when cardiopulmonary risk was separated into CV and pulmonary components, CV mortality increased while pulmonary mortality remained largely unchanged (Laden et al. 2006a, b). Similar findings

were reported from the American Cancer Society study (Pope et al. 2004) and the authors concluded that fine PM is a risk factor for CV disease caused by inflammation, atherosclerosis, and altered autonomic function. In a compelling study in which participants had coronary arteriography performed previously, ischemic cardiac events were only found among individuals with underlying coronary artery disease (Pope et al. 2006). Long-term exposure to ambient PM has been associated with changes in common carotid intimamedia thickness, especially in older populations (Künzli et al. 2005; Diez Roux et al. 2008), as well as increased coronary artery calcification (Hoffmann et al. 2007). Long-term exposure to PM was also associated with increased levels of systemic inflammatory markers such as CRP and fibrinogen (Hoffmann et al. 2009), as well as white cell counts (Chen and Schwartz 2008). Chronic exposure to PM has been associated with increased levels of endothelin-1 and elevated pulmonary arterial pressure in children living in Mexico City (Calderon-Garciduenas et al. 2007).

Diabetes

The USA is experiencing an epidemic of type 2 diabetes and its associated conditions, obesity and metabolic syndrome. In 2007, it was estimated that 26% of US adults had abnormal fasting glucose levels, or pre-diabetes. Diabetes is characterized by disturbances in cardiovascular risk factors—increased white blood cell counts and fibrinogen—and adverse vascular events. The disease is associated with endothelial dysfunction, which further increases the risk for cardiovascular events. Recent evidence links impaired endothelial cell-dependent vascular reactivity with cardiovascular events, including death, MI, and stroke. Hyperglycemia itself increases oxidative stress leading to endothelial dysfunction, lipid peroxidation, and hypercoagulablity and ultimately vascular disease. Particle-associated endothelial cell dysfunction may in part be responsible for the enhanced sensitivity of diabetics to PM.

Diabetics have been identified as a population at increased risk for effects from PM exposure, enhancing their risk of cardiovascular effects. Analysis of data from Cook County, Illinois, for the years 1988–1994 revealed that the presence of diabetes doubled the particle-associated risk for hospital admission for heart disease (Zanobetti and Schwartz 2002). A 10-$\mu g/m^3$ increase in PM_{10} was associated with a 2.01% increase in admission for heart disease with diabetes and only 0.94% increase in risk without diabetes. Similarly, a twofold higher mortality risk was associated with PM_{10} exposure for diabetics than for controls in a 2004 case-crossover study (Bateson and Schwartz 2004). O'Neill and colleagues found decreased flow-mediated reactivity in diabetes associated with SO_4 and black carbon (BC) levels (O'Neill et al. 2005). A follow-up study by these investigators observed positive associations between $PM_{2.5}$, BC, and SO_4 exposures and inflammatory markers ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) among people with type 2 diabetes (O'Neill et al. 2007). There were particularly strong associations between $PM_{2.5}$, BC, and VCAM-1 in smokers and individuals not taking statins. These types of inflammatory mechanisms may help explain the increased risk of air pollution-associated CV events among diabetics.

Evidence linking increased levels of air pollution with adverse outcomes in diabetes also comes from panel studies. Dubowsky and co-workers observed that C-reactive protein and IL-6, blood markers of systemic inflammation, increased in association with $PM_{2.5}$ exposure in elderly diabetics but not in non-diabetic, nursing home residents in St. Louis (Dubowsky et al. 2006). In Chapel Hill, Schneider et al. studied 22 type 2 diabetics ages 48–78 years (mean=61 years) on four consecutive days with daily measurements of $PM_{2.5}$ evaluating endpoints including flow-mediated dilatation, soluble blood factors, coagulation factors, and electrocardiogram parameters using Holter monitoring (Schneider et al. 2008). Among diabetics, $PM_{2.5}$ was associated with (1) an immediate decrease in flow-mediated dilatation (lag 0), (2) an acute decrease in small artery elasticity (lag 1), (3) an increase in IL-6 and TNF-α (lag 2), and (4) effects related to obesity, diabetic control, and GSTM1 genotype. In a follow-up study, Schneider et al. reported effects of short-term exposures to ambient $PM_{2.5}$ on markers of systemic inflammation, autonomic control of heart rate, and repolarization in adults with type 2 diabetes (Schneider et al. 2010b). Exposure to elevated levels of ambient fine particulate air pollution showed a wave of responses in association with $PM_{2.5}$. $PM_{2.5}$ immediately altered ventricular repolarization and potentially increased myocardial vulnerability to arrhythmias and induces systemic inflammation, which occurred 2 days later. These results suggested that some mechanisms work rapidly through physiological systems primed to respond quickly, while others required a greater length of time for the activated signaling pathways to translate the response. This study provided additional evidence that individuals with diabetes were very sensitive to $PM_{2.5}$, especially those with characteristics associated with higher insulin resistance or with oxidative stress (for example, the GSTM1 null polymorphism).

Another approach, namely, controlled clinical studies, has also provided evidence of increased susceptibility to particulate matter in diabetes. Stewart et al. conducted a randomized crossover study of 19 type 2 diabetic individuals who inhaled filtered air or 50 $\mu g/m^3$ elemental carbon (EC) ultrafine particles (UFPs) for 2 h at rest on a mouthpiece and found that exposure caused transient activation of blood platelets, with possible associated activation of blood leukocytes and vascular endothelium, in people with type 2 diabetes (Stewart et al. 2010). Furthermore, inhalation of UFPs consisting of EC, as surrogates for UFP of combustion origin, altered both pulmonary and systemic vascular function in healthy subjects (Frampton et al. 2006; Shah et al. 2008). These effects, while transient and small in magnitude, suggested an acute vascular insult with prothrombotic consequences, which could help explain the observed associations between PM exposure and acute cardiovascular effects in people with diabetes.

In summary, there is increasing evidence that inflammatory and coagulation mechanisms contribute to the increased risk for acute cardiovascular events in diabetics exposed to particulate matter. Additional support comes from animal studies using a sensitive strain of mice; exposure to ambient concentrated $PM_{2.5}$ caused insulin resistance, vascular dysfunction, and systemic inflammation. Impaired endothelial responses and oxidative stress appear to play major roles in thrombosis and accelerated atherosclerosis providing the underpinnings for the acute and chronic cardiac events. Together, these findings provide plausible mechanistic pathways by which PM exposure increases cardiovascular risk in diabetes. Ongoing studies are likely to shed additional light on the cardiovascular

consequences of exposure to particulate matter in obesity, the metabolic syndrome, and type 1 and type 2 diabetes.

Asthma

Asthma is often a disease of the young, the incidence being highest in the first 10 years of life. In fact, acute asthma is the most common medical emergency in children. The overall impact and burden of asthma on society is immense and increasing: for example, annually, there are two million emergency room visits and 0.5 million hospitalizations for asthma in the USA. In the outpatient arena, the scope is even more overwhelming with 11.3 million office visits and 2.9 million visits per year to pediatricians. In addition to the tremendous morbidity associated with asthma, there are approximately 4,000 deaths/year.

Asthma is defined as a chronic lung disease characterized by three components: (a) Airway inflammation where many cells and cellular elements play a role; the asthmatic airway is characterized by increased numbers of eosinophils, lymphocytes, and neutrophils, with destruction of the ciliated epithelium and remodeling of the subepithelial structures. The inflammatory processes are characterized as TH2 profile, in which lymphocytes and other inflammatory cells produce interleukin-4, interleukin-5, and interleukin-13, with recruitment of eosinophils into the airway mucosa; (b) airway obstruction (or narrowing), usually reversible, either spontaneously or with treatment; and (c) airway hyperresponsiveness to a variety of stimuli. The asthmatic airway constricts when challenged with specific allergens and is hyperresponsive to nonspecific irritants and aerosols. Sulfur dioxide inhalation reproducibly constricts the airways of many people with asthma and has been used as a measure of airway responsiveness.

Asthmatics are known to be susceptible to the effects of air pollution. Genetics and nutrition may contribute to asthma susceptibility and are currently under intense investigation. Other susceptibility risk factors exist. Total mass or numbers of particles deposited in the lung may be a susceptibility modifier. Respiratory diseases affect total PM deposition, distribution, and clearance. Activity levels or exercise may further increase particle deposition. People with obstructive lung diseases such as asthma or COPD often have greater deposition of fine particles in the lung than healthy people and the particles deposit more centrally in the airways, which means that some parts of the major airways may have much higher deposition of particles than others (Kim and Kang 1997). Mild asthmatics have a greater deposition of ultrafine particles than healthy people (Chalupa et al. 2004). This may partially explain why individuals with underlying airway disease are more susceptible to the respiratory effects of air pollution.

Studies have shown convincingly that during episodes of air pollution, emergency room visits and medication use in asthmatics increase, especially in children. For example, Yu and colleagues in a panel study in Seattle followed 133 children collecting 58 days of data/child and monitoring daily $PM_{2.5}$ levels (Yu et al. 2000). In their model, the population average estimates indicated an 18% (95% CI 5–33%) increase for an asthma episode for a 10-μg/m^3 increment in same day particulate matter <1.0 μm ($PM_{1.0}$) and an 11% (95% CI 3–20%) increase for a 10-μg/m^3 increment in particulate matter <10 μm (PM) lagged 1 day.

Slaughter et al. (2003) followed the same group of children, and subsequently, observed increases in $PM_{2.5}$ and PM_{10} were significantly associated with an increased risk of more severe asthma attacks and medication use in Seattle area children with asthma.

The link between diesel particle exposure and asthma has been of special interest. Studies dating to the late 1990s provided a mechanistic link between diesel particulate and allergic responses. Nasal instillation of diesel particles enhanced local mucosal IgE production and induced an inflammatory response of cells, chemokines, and cytokines detected in nasal lavage (Diaz-Sanchez et al. 1999). In comparison, the instillation of diesel particles plus allergen (1) enhanced local antigen-specific IgE production, (2) deviated cytokine production toward a TH2 profile, and (3) drove the in vivo isotype switch to IgE production. These early data triggered interest in the role of diesel in provoking asthma. And recently, McCreanor et al. carried out a panel study in London examining pulmonary responses in 60 mild and moderate asthmatics walking on separate occasions, along a street with significant diesel particulate and in a park (McCreanor et al. 2007). Participants had significantly higher exposures to fine particles (<2.5 μm in aerodynamic diameter), ultrafine particles, and elemental carbon on Oxford Street than in Hyde Park. Walking for 2 h on Oxford Street induced asymptomatic but consistent reductions in the forced expiratory volume in 1 s (FEV_1) (up to 6.1%) and forced vital capacity (FVC) (up to 5.4%) that were significantly larger than the reductions in FEV_1 and FVC after exposure in Hyde Park (P=0.04 and P=0.01, respectively). These changes were accompanied by greater increases in biomarkers of neutrophilic inflammation (sputum myeloperoxidase) on Oxford Street than in Hyde Park. The changes were associated most consistently with exposures to ultrafine particles and elemental carbon, markers of diesel exhaust.

A recent publication prepared for the Health Effects Institute summarized the findings on air pollution and asthma (Health Effects Institute 2010). The report concluded that: (1) for children, the data indicate "sufficient evidence" to infer a causal role for traffic-related pollution and asthma exacerbations. However, for asthma causation, the panel considered the evidence to be in a gray zone between "sufficient" and "suggestive but not sufficient". (2) In contrast, for adults, the existing studies provided evidence that was "suggestive but not sufficient" to infer a causal role for traffic-related pollution and asthma exacerbations. There was "insufficient evidence" to link air pollution with asthma onset. However, the evidence for an effect of air pollution and the onset of asthma in adults continues to get stronger as evidenced by a report from demonstrating a role for traffic-related pollution in adult-onset asthmatic never smokers.

In conclusion, it is not clear whether air pollution is contributing to the resurgence or persistence of airflow obstruction, or whether it is a causative factor in asthma development, particularly in longitudinal studies of pollution and asthma development that begins at school age. Although research on the genetic basis of response to air pollution is just emerging, susceptibility-determining genes may prove crucial in clarifying the link between air pollution and asthma causation and exacerbation.

Genetic and epigenetic susceptibility

Genetic susceptibility

In defining susceptibility to air pollution, one should also consider underlying genetic variation in the populations being studied. Genetic susceptibility to air pollution has been investigated in relation to respiratory health outcomes such as asthma and lung function growth. Regional and local air pollution are associated with decreased lung function growth and with asthma (Gauderman et al. 2004, 2007; Islam et al. 2007; McConnell et al. 2003, 2010), though whether the association with asthma is causal remains elusive. One explanation for the conflicting body of evidence in the literature may stem from differences in susceptibility to asthma across different study populations. It is particularly important to consider that differences in genetic variation, when addressed correctly, may help to clarify the true underlying association between air pollution exposure and asthma incidence.

Inhaled air pollutants affect several biological pathways important to lung injury and disease processes, including oxidative stress and inflammatory pathways (Peden 2001; Krishna et al. 1996; Risom et al. 2005; Menzel 1994). An individual's response to air pollution can vary greatly, in part dependent on the presence of genetic polymorphisms within these pathways.

For example, variation in antioxidant genes that protect us from pollutants can make some individuals more susceptible to harmful effects from air pollution. The most well-studied of these genes are the glutathione S-transferases (GSTs), primarily GSTM1 and GSTP1, which aid in the detoxification of numerous xeniobiotic compounds and protect cells against reactive oxygen species. In human studies of exposure to ozone and diesel exhaust particles, polymorphisms in GSTM1 and GSTP1 have been associated with increased respiratory symptoms, risk of asthma, and decreases in lung function (Yang et al. 2008). Children in Mexico City with the GSTM1 null genotype demonstrated significant ozone-related decrements in lung function (McCunney 2005). A combination of variation in microsomal epoxide hydrolase (EPHX1) and GSTP1 genes contributes to the occurrence of childhood asthma and increases asthma susceptibility to exposures from major roads (Salam et al. 2007b).

Genetic variation in GSTs also increases susceptibility to the harmful effects of environmental tobacco smoke exposure (ETS). Two common polymorphisms in GSTP1 increased the odds for ETS-related atopy (Schultz et al. 2010). Children carrying any GSTP1 Val-105 allele were at a significantly greater risk of wheeze when exposed to ETS in a dose–response manner (Lee et al. 2007). In infants exposed to in utero smoke, polymorphisms in GSTT1, GSTM1, and GSTM2 have been associated with reduced airway responsiveness, increased prevalence of early asthma and wheeze, and with decreased lung function growth in childhood, respectively (Murdzoska et al. 2010; Breton et al. 2009; Gilliland et al. 2002).

More recently, variation in GSS, the gene responsible for production of glutathione, an important antioxidant thiol, conferred differences in susceptibility for lung function growth deficits associated with air pollutants (Breton et al. 2011b). The negative effects of air pollutants were largely observed only within participants who had a particular GSS

haplotype. Variation in HMOX1, an antioxidant that provides a first line of defense in response to reactive oxygen species, has been associated with reduced risk of incident asthma in communities with low levels of ozone exposure (Islam et al. 2008). However, in communities with high ozone levels, this protective effect of the HMOX variant is lost.

Variation in metabolizing genes may also increase susceptibility to pollutant-related cellular damage. EPHX1 activity determines metabolism of some traffic pollutants, particularly polycyclic aromatic hydrocarbons. Functional variants in this gene are associated with respiratory diseases (Hersh et al. 2006). Two distinct metabolic phenotypes have been described, indicating high versus low/intermediate metabolic activity. These phenotypes are differentiated using a combination of His139Arg and Tyr113His genotypes. Children with the high metabolizer phenotype had a threefold increased odds of ever having been diagnosed with asthma compared to children with the low/intermediate metabolizer phenotype, but only if they lived within 75 m of a major road (Salam et al. 2007b). No differences in risk were observed between phenotypes in children who lived greater than 75 m from a major road. One biological reason for such an observation is that high metabolizers process oxidants faster which may lead to increased oxidative damage in cells and a higher risk of asthma.

Genetic variation in transforming growth factor (TGFβ1), a gene involved in airway remodeling and inflammation, is also associated with differences in susceptibility to effects of traffic-related emissions on early persistent asthma (Salam et al. 2007a). Traffic emissions induce airway inflammation and modulate TGFβ1 gene expression (Dai et al. 2003). The C-509T polymorphism in the TGFβ1 gene promoter is a functional SNP that has been associated with increased gene expression and plasma concentrations (Silverman et al. 2004; Grainger et al. 1999). Children with the −509TT genotype living within 500 m of a freeway had over threefold increased lifetime asthma risk compared with children with CC/CT genotype living greater than 1,500 m from a freeway (Salam et al. 2007b).

The genes highlighted above are recent examples, but not the only ones, illustrating how genetic variation is associated with susceptibility to air pollution on respiratory health outcomes. Two recent reviews provide further and more detailed examples of genetic susceptibility to air pollution in the context of respiratory health outcomes (London and Romieu 2009; Yang et al. 2008).

Epigenetic susceptibility

While genetic polymorphisms present concrete changes to the genetic code that may permanently alter gene expression, potentially reversible alterations to the epigenome that do not involve alterations to the DNA sequence may also play a role in defining individual susceptibility to pollutants. Such epigenetic alterations, which include DNA methylation and histone modifications, play a critical role in gene expression and cellular function (Goldberg et al. 2007) and may also be responsive to environmental stimuli (Bollati and Baccarelli 2010; Dolinoy and Jirtle 2008; Jirtle and Skinner 2007).

In the last few years, evidence that air pollution is associated with DNA methylation levels has begun to surface. Most of the early research in humans focused on the effects of air

pollution in the DNA repetitive elements, LINE1 and Alu. PM, black carbon, and benzene have all been associated with modest decreases in LINE1 and/or Alu methylation (Baccarelli and Bollati 2009; Madrigano et al. 2011). Some of these air pollution-related differences in DNA methylation in repetitive elements have also been associated with cardiovascular health outcomes such as ischemic heart disease and stroke (Baccarelli et al. 2010a, b).

Investigation of the association between air pollutants and gene-specific CpG loci, primarily in promoter regions of genes believed to be important to various disease processes, has also begun, aided by the advent of large array-based platforms of methylated CpG targets. Evidence is emerging to support a role for epigenetics in the development and persistence of asthma and allergic rhinitis (North and Ellis 2011; Ho 2010), and variation in epigenetics may increase certain individuals' susceptibility to air pollution-related respiratory disease. Increased exposure to ambient air pollution has been associated with several genes believed to be important in asthma. Hypermethylation of the Foxp3 locus and impairment of Treg cell function was observed in response to elevated ambient pollution levels (Nadeau et al. 2010), and methylation in the ACSL3 gene in offspring was associated with exposure to polyaromatic hydrocarbon during pregnancy (Perera et al. 2009). Particulate matter was also associated with decreases in DNA methylation in NOS2A, a gene directly responsible for production of nitric oxide, an important player in both respiratory and cardiovascular diseases (Tarantini et al. 2009; Breton et al. 2011a).

Moreover, the Agouti mouse model has been successfully used to screen various toxicological agents for detrimental effects on the epigenome and has demonstrated the usefulness of dietary supplementation as a potential intervention to protect against the epigenetic effects (Dolinoy and Jirtle 2008). Although to date this model has not been applied to air pollutant exposures, one could easily conceive of an experiment to do so, in which interventions could also be explored.

The field of environmental epigenetics is new and holds substantial promise for advancing our understanding of how environmental exposures such as air pollution affect cardiorespiratory health outcomes. Exciting scientific questions remain unanswered, such as whether epigenetic alterations can affect individual susceptibility, either to air pollution exposure or to risk of cardio-respiratory and other diseases, and whether genetic and epigenetic variation can jointly affect individual susceptibility. As technological advances make it possible and affordable to identify epigenetically labile loci throughout the genome, the use of key loci for screening and diagnostic tools will become increasingly feasible at a population level to identify individuals or groups of individuals with greater susceptibility either to environmental exposures or to specific diseases.

Identification of populations particularly susceptible to air pollution, the degree of their sensitivity to exposure, and their frequency in the population are important objectives in order to target future preventive strategies. Unlike genetic polymorphisms, DNA methylation alterations are not permanent and thus may present a good opportunity for population intervention such as exposure reduction, dietary modification, or use of medication.

Applications and future directions in susceptibility research

As the previous syntheses of knowledge suggest, the evidence that cardiovascular disease, diabetes, asthma, and genetic and epigenetic factors are important indicators of susceptibility to air pollution is growing. In addition to the ubiquity of exposure to air pollution, the public health relevance of this issue is underscored when one takes into account the size of the affected populations. According to the 2009 U.S. National Health Interview survey, 12% of adults had ever been told by a doctor that they had heart disease, 13% that they had asthma, and 9% that they had diabetes (Centers for Disease Control and Prevention 2010). In other words, the population affected by these conditions is in the tens of millions. With regard to genetics, the frequency of the variant genotype in some of the identified susceptibility genes ranges up to 40–50%.

Understanding population susceptibility to air pollutants is critical for forming policies that can yield maximal population health benefits. The literature previously discussed focused on disease status and biomedical characteristics and responses of the individual. In the 2006 global update of WHO air quality guidelines, attempts were made to grapple with the question of how we consider susceptibility in air quality regulation, with chapters on the concept of susceptibility as well as environmental equity (WHO 2006a). The WHO panel concluded that the state of the scientific knowledge with regard to environmental equity susceptibility was not sufficient to address this concept in generally, globally applicable air quality guidelines. Since that time, some of the gaps in knowledge regarding environmental equity have been filled, but many remain and the location-specific differences in findings continue to reinforce the idea that overall air quality guidelines are likely to focus on biomedical and demographic susceptibilities to define populations at risk.

One area of inquiry related to susceptibility that has been receiving increasing attention is air pollution's potential influence on perinatal health. Air pollution's influence on birth outcomes has tremendous implications for population health, since early life experiences and disadvantages may have adverse effects persisting across the life course. Many of the same mechanisms of action, including genetic and epigenetic factors that have been evaluated for chronic diseases such as asthma, and the mechanisms by which air pollution may contribute to CV (e.g., oxidative stress) are likely to play a role in observed associations between pollution exposure and outcomes, including preterm birth and low birth weight. Recent reviews highlight current knowledge and methodological needs for evaluating these and other reproductive outcomes (Slama et al. 2008; Ritz and Wilhelm 2008).

A final emerging area of inquiry is the connection between air pollution exposure and land use and urban infrastructure design. Understanding health effects, mechanisms, and susceptibility are critically important, but the interventions that ultimately result in air pollution reductions are what improve population health. A recent international workshop on this topic concluded that reduction of the burden of CV disease and inclusion of air pollution considerations in land use planning are two potentially powerful and wide-ranging interventions that can reduce health impacts, both among susceptible populations and the population as a whole (Giles et al. 2010).

The research on susceptibility to air pollution that we have discussed provides important insights on the biological mechanisms at play and reinforces the need to continue reducing air pollution exposures to enhance health. To echo the quote with which we began, we continue to see evidence that it is those who are in the "dawn of life, the children; those who are in the twilight of life, the aged; and those who are in the shadow of life…" who are at highest risk from exposures to air pollution.

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Abbreviations

ANS	Autonomic nervous system
BC	Black carbon
CAPS	Concentrated ambient air particles
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular
EC	Elemental carbon
EPHX1	Microsomal epoxide hydrolase
HMOX1	Heme oxygenase
HRV	Heart rate variability
MI	Myocardial infarction
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
PM	Particulate matter
UFPs	Ultrafine particles
WHO	World Health Organization

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