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**Air Pollution and Non-Communicable Diseases: A Review by
the Forum of International Respiratory Societies'
Environmental Committee, Part 1: The damaging effects of
air pollution**

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Air Pollution and Non-Communicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part**1: The damaging effects of air pollution**

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Abstract

Air pollution poses a great environmental risk to health. Outdoor fine particulate matter (PM_{2.5}) exposure is the fifth leading risk factor for death in the world, accounting for 4.2 million deaths and more than a hundred million disability-adjusted-life-years lost according to the Global Burden of Disease Report. The World Health Organization attributes 3.8 million additional deaths to Indoor air pollution. Air pollution can harm acutely, usually manifested by respiratory or cardiac symptoms, as well as chronically, potentially affecting every organ in the body. It can cause, complicate, or exacerbate many adverse health conditions. Tissue damage may result directly from pollutant toxicity, because fine and ultrafine particles can gain access to organs, or indirectly through systemic inflammatory processes. Susceptibility is partly under genetic and epigenetic regulation. Although air pollution affects people of all regions, ages, and social groups, it is likely to cause greater illness in those with heavy exposure and greater susceptibility. Persons are more vulnerable to air pollution if they have other illnesses or less social support. Harmful effects occur on a continuum of dosage and even at levels below air quality standards previously considered to be safe.

Introduction

Air pollution may be the greatest environmental risk to health in the world (1). According to the Global Burden of Disease estimates, one component of ambient (or outdoor air) pollution, fine particulate matter, or $PM_{2.5}$, is the fifth leading risk factor for death in the world, accounting for 4.2 million deaths (7.6% of total global deaths) and more than 103 million disability-adjusted-life-years-lost in 2015. Exposure to ambient ozone (O_3) caused an additional 254,000 deaths (2), and estimates by other statistical techniques set these numbers even higher (3). The World Health Organization reported that indoor air pollution from fires for cooking and heating accounted for 3.8 million deaths; this number ranged from 10% in low and middle income countries to 0.2% in high income countries (4). In almost all cases, the greatest affliction of air pollution falls on the vulnerable.

Air pollution may be associated with symptoms immediately upon exposure, such as coughing, tearing, difficulty breathing, and angina. It may also be associated with long-term harm that is more subtle. People are usually unaware of how long-term exposure affects their health or worsens their medical problems over time. Polluted air gains access to the body through the respiratory tract but has systemic effects that can damage many other organs.

The main purpose of these 2 papers is to review the available evidence to support the hypothesis that air pollution affects many organs beyond the lungs. The review omits infectious diseases and tobacco smoke exposure, and it generally does not distinguish between ambient and indoor

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3 (household) air pollution, although they can have very different compositions. Tobacco smoke could be considered a form of high dose air
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5 pollution. There are similarities between tobacco smoke and air pollution in how they injure the body; and their harmful health effects become
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7 increasingly similar as the toxicity and dosages of the inhaled materials become more alike. However, the lung disease resulting from exposure
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9 to indoor smoke has more bronchitic and less emphysematous elements than tobacco smoking (5). In Part I of this report, we review the
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11 mechanisms and multi-system health effects of air pollution in general and among vulnerable populations. In Part II, we review the evidence for
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13 air pollution's effects on individual organ systems.
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16 17 18 **What air pollution is and how it causes illness** 19 20

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23 Air pollution is defined as any substance in the air that may harm humans, animals, vegetation, or materials (6). Pollutants come from various
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25 sources and each can have differing characteristics depending on the composition, source, and conditions under which they were produced.
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27 Common gases include the sulfur oxides (mainly sulfur dioxide, SO₂), nitrogen oxides (mainly nitric oxide, NO, and nitrogen dioxide, NO₂),
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29 reactive hydrocarbons (often referred to as volatile organic compounds), and carbon monoxide (CO). They are released directly into the
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31 atmosphere, usually from industrial or transportation sources, and are called "primary pollutants." Gaseous and particle pollutants can also form
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33 in the atmosphere, largely from the primary pollutants and are called "secondary pollutants." For example, ozone (O₃) is formed from nitrogen
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35 oxides and hydrocarbons in the atmosphere; sulfuric acid is produced from atmospheric sulfur; and ammonium nitrate aerosols are created from
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37 atmospheric nitrogen oxide gases.
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5 The damage to human tissue by gases depends on their water solubility, concentration, ability to oxidize tissue, and the affected person's
6 susceptibility. Sulfur dioxide (SO₂) is highly soluble in water and largely damages the upper airways and skin, while NO₂ and O₃ are less soluble
7 and therefore can penetrate deeper into the lung. Carbon monoxide is highly soluble and nonirritating and readily passes into the blood stream.
8 Its toxicity mainly results from successfully competing with oxygen in binding to hemoglobin, which results in tissue hypoxia. Its effects are
9 acute—a 2-day increase of mean CO levels of 1 mg/m³ was associated with a 1.2% increase in total deaths in a large European study (7). Nitric
10 oxide also attaches to hemoglobin and other iron containing proteins, but it generally acts only a short distance from its contact point because of
11 its binding affinity.
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23 Particulate matter is usually classified by its size or aerodynamic diameter; PM₁₀ denotes particles smaller than 10 micrometers (μm); PM_{2.5}
24 particles are smaller than 2.5 μm; and PM_{0.1} particles are smaller than 0.1 μm in diameter. All PM_{2.5} and PM_{0.1} are included in PM₁₀. Therefore,
25 adverse effects attributed to PM₁₀ could be caused by smaller particles. The term “coarse particles” is used to refer to particulates between PM₁₀
26 and PM_{2.5} in size. In contrast to large particles that can be visible as dust or haze with appropriate lighting, small particles are invisible. Large
27 particles may affect mucous membranes and the upper airways, causing cough and tearing. Fine particles (PM_{2.5}) easily find their way into lung
28 alveoli, and ultrafine particles (PM_{0.1}) pass through the alveolar-capillary membrane, are readily picked up by cells, and carried via the blood
29 stream to expose virtually all cells in the body. Smaller particles, therefore, have greater systemic toxicity (see table).
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3 Beyond its size, the harm caused by particulate matter relates to its structure and composition. For example, particles that are highly acidic are
4 more noxious. Toxic components may lie on the particle's surface and be responsible for the tissue damage on contact. Toxic "hitch-hikers,"
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6 elements such as arsenic, lead, or cadmium, or compounds such as sulfuric acid or polycyclic aromatic hydrocarbons, can be picked up during
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8 the combustion process and be carried deep into the lung on the surface of the ultrafine particles. This is most relevant to particles resulting
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10 from fossil fuel combustion, especially coal combustion, which contains many heavy metal components and high levels of sulfur. If similar-sized
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12 particles do not contain as many toxic add-ons, they generally cause less harm (8). Particulate matter, however, can also interact with airborne
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14 allergens as hapten carriers to trigger or even induce allergic asthma reactions in sensitized subjects (9).
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21 In addition to encroaching on an organ and causing direct harm, exposure to pollutants, including toxic metals, organic compounds and gases,
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23 can cause inflammation with systemic effects. The inflammation, usually in the lung, causes oxidative stress. Oxidative stress entails lipid
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25 peroxidation, depletion of antioxidants, and activation of pro-inflammatory signaling. The pro-inflammatory signaling sets off a cascade of
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27 events that may affect distant organs. The greater the surface area of ultrafine particles, the greater the ability to produce oxidative stress (10).
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29 Increases in particulate exposure are associated with elevated C-reactive protein, fibrinogen, circulating blood leukocytes and platelets, and
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31 plasma viscosity (11). Leukocytes, adhesion proteins, clotting proteins, and an array of cytokines and inflammatory mediators tax the
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33 endothelium, which may lose its modulating function (12). Repeated insults from pollution can contribute to vascular conditions, such as
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35 atherosclerosis, and can have a wide range of effects on metabolism. Ultrafine particles that go directly into different organs also can be
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37 responsible for inflammation in that organ (13).
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5 In addition, the lung faces the damaging effects of filtering particulate matter and accumulation of “soot” in the lungs if the clearance
6 mechanisms cannot handle the load. The sheer volume of particulate matter may overwhelm macrophage function and the lymphatic system
7 leaving deposits of material centered around the terminal bronchioles and early generation respiratory bronchioles (14) (figure 1). The
8 particulate burden may lead to chronic focal inflammation and fibrosis, and could predispose to “scar” lung carcinoma (15). The efficiency of
9 particulate clearance is a factor in how pollution affects the body.
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19 The immune and inflammatory responses to air pollutants may be genetically regulated. Many important genes involve inflammation and
20 variation in glutathione synthesis (16). Genetic variation in the glutathione pathway been reported to increase susceptibility to pollution-related
21 lung function decrements in children (17). Variations in genes that control inflammatory mediators, which include toll-like receptor 4 (TLR₄),
22 tumor necrosis factor- α (TNF α), transforming growth factor- β (TGF- β ₁), and many others, have been found to increase susceptibility to the
23 respiratory effects of pollution (16). Air pollutants affect both the innate and adaptive immune systems. Particulate matter disturbs the balance
24 of the Th1 and Th2 leukocyte populations, resulting in dominant Th2 leukocytes, which is a feature of asthma (18).
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34 Epigenetics refers to potentially reversible modifications to DNA that control how genes are expressed, without altering the DNA sequence.
35 Epigenetics mediate genetic and physiological responses to air pollution and are, therefore, an important cause of susceptibility to pollution-
36 related health effects (19). Changes in micro-RNA and other RNA species also regulate gene expression, often through signaling pathways. Air
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3 pollution exposure may affect these epigenetic processes (20). Cord blood samples from several birth cohort studies, showed prenatal NO₂
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5 exposure was associated with DNA methylation in several mitochondria-related genes, as well as several genes involved in antioxidant defense
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7 pathways (21) Figure 2 shows different ways that air pollution can mediate tissue damage.
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10 11 12 **Air pollution and exercise** 13

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16 Physical exertion that results in increased ventilation and mouth breathing augments inhalation of air pollutants. In athletes who stress their
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18 ventilatory and cardiac reserves, pollution exposure has been found to decrease exercise performance. Maximal oxygen consumption and
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20 exercise duration are decreased with exposure to CO (22). Experimental exposure to O₃ reduces the exercise capacity of athletes and leads to a
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22 transient decrease in spirometric function (23). Increased ambient PM₁₀ concentrations are associated with reduced marathon performance in
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24 women (24). Despite these harmful effects, studies suggest that the health benefits of exercise outweigh the adverse effects of pollution
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26 exposure during exercise (25) in all but the most polluted areas (26).
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31 32 **Sleep** 33 34 35 36 37 38 39 40 41 42 43 44

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3 Sleep efficiency is decreased in most polluted areas, especially with increased exposure to NO₂ and PM (27). Several studies show that air
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5 pollution is associated with increased sleep apnea symptoms, possibly because of upper airway inflammation from irritant pollutants and
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7 airborne allergens (28) and household biomass smoke (29).
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12 Air pollution may affect sleep adversely in other ways. Traffic-related air pollution is highest near busy streets, which confounds sleep studies
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14 because the environment is more often noisy and illuminated. Pollution may also disturb sleep by exacerbating asthma, COPD, or other
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16 respiratory or chronic diseases. In addition, pollutants may lead to an inflammatory reaction in the central nervous system or directly interfere
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18 with neuronal function that may affect sleep (30).
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23 **Children**

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28 Children are especially harmed by air pollution for both environmental and biological reasons. Children breathe more air per unit body weight
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30 and, therefore, inhale more airborne toxicants than adults exposed to the same amount of air pollution. In many parts of the world where
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32 biomass is burned indoors for cooking and heating, small children are heavily exposed to indoor air pollution along with their mothers. Children
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34 all over the world generally spend more time outdoors and are more physically active than adults, which can result in greater exposure to
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36 outdoor air pollution.
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3 Children are biologically more susceptible to pollution because their bodies are still not mature. Lung and immune system development occurs
4 over the entire prenatal period, beginning with embryogenesis and continuing for many years after birth. Infants are born with only about 20%
5 of the alveoli that they will eventually make once they have reached adulthood. Exposures to air pollutants during the prenatal period and
6 during childhood can have harmful and irreversible effects on the lung and other organ systems.
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14 Post-natal exposures to air pollutants, including PM, O₃, and NO₂, have been associated with increased infant mortality, even in developed
15 countries, such as the United States. The strongest associations have been with post-neonatal respiratory mortality (31) (32) (33), which in part
16 may be related to respiratory infections that have links to pollution (34). Air pollution may be a “second hit” in newborns who are susceptible to
17 infection because of their immature immune systems. Post-natal diesel pollution exposure also has been found to attenuate the lung’s immune
18 response to respiratory infection and to augment the inflammatory response, which likely results in a worse course of illness (35).
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28 Air pollution has also been found to affect growth trajectories of the lung and its function during childhood, which can affect the level of
29 respiratory health achieved in adulthood. PM_{2.5} exposure has been found to impair pre- and post-natal development of tracheobronchial tree
30 (36). Many studies have found that higher exposure to PM and traffic are linked to worse lung function in childhood, and slower child lung
31 function growth (37) (38) (39), which, in turn, may limit lung function in adulthood (40). Long-term pollution exposure during childhood,
32 especially traffic-related pollution, has been associated with risk of developing childhood asthma (41) (42) and is another example of how
33 pollution exposure during childhood affects organ development and risk of subsequent chronic disease.
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Maternal-fetal health and reproductive health

Exposure to air pollution during pregnancy is associated with adverse pregnancy outcomes and reduced fetal growth. A review of more than 13,000 pregnancies in Scotland found that exposure to higher levels of PM_{2.5}, PM₁₀, and NO₂, were associated with lower infant head size during pregnancy and at birth (43). Another study across all trimesters of pregnancy showed the risk of intrauterine growth restriction was increased among women exposed to higher levels of CO, NO₂, and PM_{2.5} (44). A meta-analysis that included nearly 3 million births across 14 centers from 9 developed countries found that, after adjusting for socioeconomic status, maternal exposure to particulate air pollution was associated with a higher risk of low birth weight infants (45).

While many studies measure air pollution exposures over the entire course of pregnancy, it is thought that exposure in the first trimester of pregnancy poses a greater risk than subsequent exposures. A study of nearly 30,000 term single births in Japan found that exposure to pollutants over the course of the entire pregnancy was not associated with fetal growth restriction. However, when they examined exposures in the first trimester, O₃ exposure was associated with higher odds of small for gestational age and low birth weight infants (46). Another study of more than 5,000 mother-child pairs of the Boston Birth Cohort and found that women who were exposed to the highest levels of PM were more likely to have intrauterine inflammation (47) compared to those exposed to the lowest levels. The risk was highest for exposures measured in the first trimester of pregnancy.

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5 Air pollution increases the risk of preterm birth and low birth weight independently and additively to other known risk factors, such as lower
6 socioeconomic status, diabetes, hypertension, and smoking (48). Women who are exposed to higher levels of traffic-related air pollution during
7 pregnancy appear to be at increased risk of preeclampsia, which may be one mechanism explaining the association with preterm birth (49). Also,
8 increased exposure to O₃ and PM_{2.5} within 5 hours of delivery has been linked to higher risk of premature rupture of membranes, which
9 predisposes women to preterm delivery (50). These adverse effects on pregnancy and birth outcomes have been observed even at relatively low
10 levels of air pollution exposure. They are especially concerning because preterm birth, low birthweight and small for gestational age infants are
11 at increased risk of a variety of health problems—including reduced lung growth and cognitive problems—that can persist for their lifetimes. On
12 the other hand, reducing air pollution has prompt benefits. When measures were taken to effectively reduce air pollution during the 2008
13 Beijing Olympic Games, there was an improvement in infant birth weight in association with the reduction in NO₂, a marker of traffic-related air
14 pollution (51).
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30 **Fertility**

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34 Several studies have found that air pollution is associated with reduced fertility rates and increased risk of miscarriage. A Mongolian study found
35 a dose-dependent relationship between the monthly average SO₂, NO₂, CO, PM₁₀, and PM_{2.5} levels during pregnancy and risk of spontaneous
36 abortions (52). A few studies have shown or suggested that semen or sperm quality is decreased in areas of high pollution (53) (54).
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Vulnerable populations

Although air pollution affects people of all regions, ages, and social and economic groups, it is more likely to cause ill health and death in certain individuals. Exposures to air pollution and other environmental factors and biological susceptibility are the most important factors determining response. People living in Africa, Asia, and the Middle East on average breathe higher levels of pollutants than those in other parts of the world (1) and, therefore, sustain a greater health burden.

Both extrinsic and intrinsic factors determine vulnerability to adverse health effects from exposures to air pollution. The most important is the level of exposure. People of low social and economic status often have greater exposures to air pollution because they live in areas of greater traffic density and near point sources of pollution such as power plants and industrial facilities. Other extrinsic neighborhood factors that contribute to vulnerability include poor housing, the lack of stores to purchase healthy food (e.g., fruits and vegetables that contain antioxidants), violent crime, segregation, lack of green space, and poor access to health care (55). Poorer people are also more likely to work in dirty jobs with occupational exposures to vapors, dusts, gases, and fumes (56). Intrinsic factors that increase vulnerability to air pollution include age (very young and very old), pre-existing disease, pregnancy, genetic and epigenetic variation, smoking, and obesity (57) (58). The concept of cumulative risk combines both extrinsic and intrinsic factors when attempting to assess vulnerability of an individual or a population to the ill-effects of air pollution.

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5 When factors are combined, the effects can be additive or multiplicative. For example, pre-existing cardiopulmonary diseases and diabetes
6 increase susceptibility to the effects of particulate air pollution (58). Psychosocial stress interacts with exposure to traffic-related air pollution to
7 increase the risk of new-onset asthma in children (59) (60). It may also enhance the effects of particulate pollution on blood pressure (61). The
8 association between air pollution and cancer risk has been shown to be greater in neighborhoods with higher levels of ethnic minority
9 segregation, an indicator that may capture the cumulative impact of multiple adverse social and psychosocial exposures (62).
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19 Impoverished individuals, especially ethnic minorities, are more likely to live in segregated neighborhoods that are near sources of pollution and
20 busy roadways. Consequently, they are more often exposed to higher concentrations of outdoor air pollutants than persons with higher
21 economic status (58). They are also likely to have greater cumulative health risks from other detrimental neighborhood factors. In low-income
22 countries, women, small children, and rural residents are likely to be exposed to higher concentration of household air pollutants during cooking
23 and heating activities (63).
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33 Vulnerability is made worse by health inequality and environmental injustice (64). Proponents of environmental justice argue that investigators
34 and regulatory agencies should evaluate the cumulative impacts of environmental and social stressors in research studies and regulatory
35 policies. Pollutant and source-specific assessments of potential health risks of air pollution do not inherently reflect the multiple environmental
36 and social stressors faced by vulnerable communities that can interact to harm health. Reducing vulnerability across a population calls for
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3 reducing poverty, segregation, and health-damaging neighborhood environmental factors as well as reducing the ambient levels of pollutants.
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5 Strategies to achieve health equality for vulnerable communities require societal commitment of resources as well as the promulgation of air
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7 quality control measures (65).
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Table. How different types of air pollution damage tissue

Pollutant	Injury determinants	Tissue affected
Sulfur dioxide (SO ₂)	Highly soluble	Upper airway and skin damage
Nitrogen dioxide (NO ₂) Ozone (O ₃) Carbon monoxide (CO)	Less soluble (NO ₂ and O ₃ are irritating)	Deeper lung penetration Bronchial and bronchiolar injury CO: Tissue hypoxia
Particulate matter (PM ₁₀ , PM _{2.5} , PM _{0.1})	Size, structure, and composition determine toxicity	Large particles: mucous membranes, upper airways Small particles: bronchioles and alveoli Ultrafine particles: systemic tissue reactions

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Legends for figures

Figure 1. Anthracotic lung. Inhaled particulates are usually cleared through the respiratory mucociliary apparatus and scavenged by alveolar macrophages. Particles can move into the interlobular septal lymphatics and be cleared by the lymphatic system, but if these mechanisms are overwhelmed, particulates may clog lymphatics and be deposited in the lung interstitium. Ultrafine particles gain entrance to mobile cells and can be transported to all parts of the body. Although this anthracotic lung is characteristic of smokers and workers in dusty occupations, anthracotic deposits are often found in urban dwellers from air pollution.

Figure 2. Pollution damage by systemic inflammation. This scanning electron micrograph of the terminal and respiratory bronchioles are the sites where most material accumulates making it the area of the lung most vulnerable to pollution. In addition, this figure depicts 4 ways that pollution can affect all organs through systemic inflammation. Ultrafine particles pass through the alveolar-capillary membrane, are endocytosed, and distributed throughout the body. They induce similar inflammatory reactions in other organs. (Copyright reserved Dean Schraufnagel)

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Figure 1. Anthracotic lung. Inhaled particulates are usually cleared through the respiratory mucociliary apparatus and scavenged by alveolar macrophages. Particles can move into the interlobular septal lymphatics and be cleared by the lymphatic system, but if these mechanisms are overwhelmed, particulates may clog lymphatics and be deposited in the lung interstitium. Ultrafine particles gain entrance to mobile cells and can be transported to all parts of the body. Although this anthracotic lung is characteristic of smokers and workers in dusty occupations, anthracotic deposits are often found in urban dwellers from air pollution.

56x94mm (200 x 200 DPI)

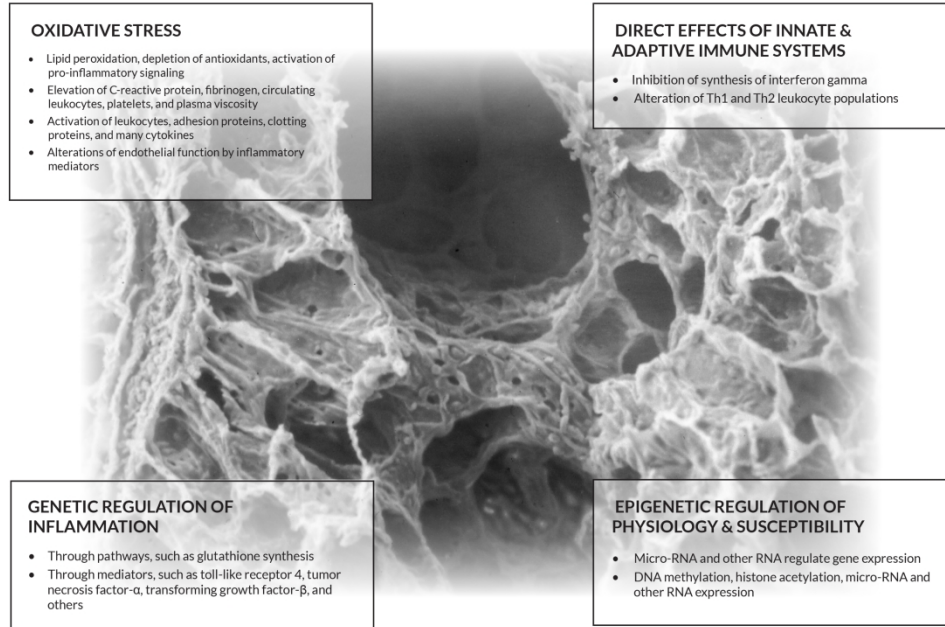


Figure 2. Pollution damage by systemic inflammation. This scanning electron micrograph of the terminal and respiratory bronchioles are the sites where most material accumulates making it the area of the lung most vulnerable to pollution. In addition, this figure depicts 4 ways that pollution can affect all organs through systemic inflammation. Ultrafine particles pass through the alveolar-capillary membrane, are endocytosed, and distributed throughout the body. They induce similar inflammatory reactions in other organs. (Copyright reserved Dean E. Schraufnagel)

Air Pollution and Non-Communicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part

1: The damaging effects of air pollution

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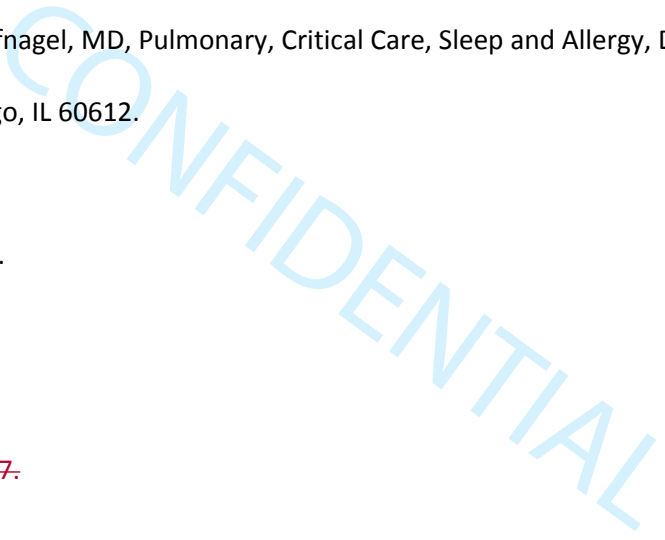
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Abstract

Air pollution poses a great environmental risk to health. Outdoor fine particulate matter (PM_{2.5}) exposure is the fifth leading risk factor for death in the world, accounting for 4.2 million deaths and more than a hundred million disability-adjusted-life-years lost according to the Global Burden of Disease Report. The World Health Organization attributes 3.8 million additional deaths to Indoor air pollution. Air pollution can harm acutely, usually manifested by respiratory or cardiac symptoms, as well as chronically, potentially affecting every organ in the body. It can cause, complicate, or exacerbate many adverse health conditions. Tissue damage may result directly from pollutant toxicity, because fine and ultrafine particles can gain access to organs, or indirectly through systemic inflammatory processes. Susceptibility is partly under genetic and epigenetic regulation. Although air pollution affects people of all regions, ages, and social groups, it is likely to cause greater illness in those with heavy exposure and greater susceptibility. Persons are more vulnerable to air pollution if they have other illnesses or less social support. Harmful effects occur on a continuum of dosage and even at levels below air quality standards previously considered to be safe.

Introduction

Air pollution may be the greatest environmental risk to health in the world (1). According to the Global Burden of Disease estimates, one component of ambient (or outdoor air) pollution, fine particulate matter, or PM_{2.5}, is the fifth leading risk factor for death in the world, accounting for 4.2 million deaths (7.6% of total global deaths) and more than 103 million disability-adjusted-life-years-lost in 2015. Exposure to ambient ozone (O₃) caused an additional 254,000 deaths (2), and estimates by other statistical techniques set these numbers even higher (3).

The World Health Organization reported that indoor air pollution from fires for cooking and heating accounted for 3.8 million deaths; this number ranged from 10% in low and middle income countries to 0.2% in high income countries (4). In almost all cases, the greatest affliction of air pollution falls on the vulnerable.

Air pollution may be associated with symptoms immediately upon exposure, such as coughing, tearing, difficulty breathing, and angina. It may also be associated with long-term harm that is more subtle. People are usually unaware of how long-term exposure affects their health or worsens their medical problems over time. Polluted air gains access to the body through the respiratory tract but has systemic effects that can damage many other organs.

The main purpose of these 2 papers is to review the available evidence to support the hypothesis that air pollution affects many organs beyond the lungs. The review omits infectious diseases and tobacco smoke exposure, and it generally does not distinguish between ambient and indoor

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3 (household) air pollution, although they can have very different compositions. Tobacco smoke could be considered a form of high dose air
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5 pollution. There are similarities between tobacco smoke and air pollution in how they injure the body; and their harmful health effects become
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7 increasingly similar as the toxicity and dosages of the inhaled materials become more alike. However, the lung disease resulting from exposure
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9 to indoor smoke has more bronchitic and less emphysematous elements than tobacco smoking (5). In Part I of this report, we review the
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11 mechanisms and multi-system health effects of air pollution in general and among vulnerable populations. In Part II, we review the evidence for
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13 air pollution's effects on individual organ systems.
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19 **What air pollution is and how it causes illness**

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23 Air pollution is defined as any substance in the air that may harm humans, animals, vegetation, or materials (6). Pollutants come from various
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25 sources and each can have differing characteristics depending on the composition, source, and conditions under which they were produced.
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27 Common gases include the sulfur oxides (mainly sulfur dioxide, SO₂), nitrogen oxides (mainly nitric oxide, NO, and nitrogen dioxide, NO₂),
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29 reactive hydrocarbons (often referred to as volatile organic compounds), and carbon monoxide (CO). They are released directly into the
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31 atmosphere, usually from industrial or transportation sources, and are called "primary pollutants." Gaseous and particle pollutants can also form
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33 in the atmosphere, largely from the primary pollutants and are called "secondary pollutants." For example, ozone (O₃) is formed from nitrogen
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35 oxides and hydrocarbons in the atmosphere; sulfuric acid is produced from atmospheric sulfur; and ammonium nitrate aerosols are created from
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37 atmospheric nitrogen oxide gases.
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5 The damage to human tissue by gases depends on their water solubility, concentration, ability to oxidize tissue, and the affected person's
6 susceptibility. Sulfur dioxide (SO₂) is highly soluble in water and largely damages the upper airways and skin, while NO₂ and O₃ are less soluble
7 and therefore can penetrate deeper into the lung. Carbon monoxide is highly soluble and nonirritating and readily passes into the blood stream.
8 Its toxicity mainly results from successfully competing with oxygen in binding to hemoglobin, which results in tissue hypoxia. Its effects are
9 acute—a 2-day increase of mean CO levels of 1 mg/m³ was associated with a 1.2% increase in total deaths in a large European study (7). Nitric
10 oxide also attaches to hemoglobin and other iron containing proteins, but it generally acts only a short distance from its contact point because of
11 its binding affinity.
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23 Particulate matter is usually classified by its size or aerodynamic diameter; PM₁₀ denotes particles smaller than 10 micrometers (μm); PM_{2.5}
24 particles are smaller than 2.5 μm; and PM_{0.1} particles are smaller than 0.1 μm in diameter. All PM_{2.5} and PM_{0.1} are included in PM₁₀. Therefore,
25 adverse effects attributed to PM₁₀ could be caused by smaller particles. The term “coarse particles” is used to refer to particulates between PM₁₀
26 and PM_{2.5} in size. In contrast to large particles that can be visible as dust or haze with appropriate lighting, whereas small particles are usually
27 invisible. Large particles may affect mucous membranes and the upper airways, causing cough and tearing. Fine particles (PM_{2.5}) easily find their
28 way into lung alveoli, and ultrafine particles (PM_{0.1}) pass through the alveolar-capillary membrane, are readily picked up by cells, and carried via
29 the blood stream to expose virtually all cells in the body. Smaller particles, therefore, have greater systemic toxicity (see table).
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3 Beyond its size, the harm caused by particulate matter relates to its structure and composition. For example, particles that are highly acidic are
4 more noxious. Toxic components may lie on the particle's surface and be responsible for the tissue damage on contact. Toxic "hitch-hikers,"
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6 elements such as arsenic, lead, or cadmium, or compounds such as sulfuric acid or polycyclic aromatic hydrocarbons, can be picked up during
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8 the combustion process and be carried deep into the lung on the surface of the ultrafine particles. This is most relevant to particles resulting
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10 from fossil fuel combustion, especially coal combustion, which contains many heavy metal components and high levels of sulfur. If similar-sized
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12 particles do not contain as many toxic add-ons, they generally cause less harm (8). Particulate matter, however, can also interact with airborne
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14 allergens as hapten carriers to trigger or even induce allergic asthma reactions in sensitized subjects (9).
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21 In addition to encroaching on an organ and causing direct harm, exposure to pollutants, including toxic metals, organic compounds and gases,
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23 can cause inflammation with systemic effects. The inflammation, usually in the lung, causes oxidative stress. Oxidative stress entails lipid
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25 peroxidation, depletion of antioxidants, and activation of pro-inflammatory signaling. The pro-inflammatory signaling sets off a cascade of
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27 events that may affect distant organs. The greater the surface area of ultrafine particles, the greater the ability to produce oxidative stress (10).
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29 Increases in particulate exposure are associated with elevated C-reactive protein, fibrinogen, circulating blood leukocytes and platelets, and
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31 plasma viscosity (11). Leukocytes, adhesion proteins, clotting proteins, and an array of cytokines and inflammatory mediators tax the
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33 endothelium, which may lose its modulating function (12). Repeated insults from pollution can contribute to vascular conditions, such as
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35 atherosclerosis, and can have a wide range of effects on metabolism. Ultrafine particles that go directly into different organs also can be
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37 responsible for inflammation in that organ (13).
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6 In addition, the lung faces the damaging effects of filtering particulate matter and accumulation of “soot” in the lungs if the clearance
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8 mechanisms cannot handle the load. The sheer volume of particulate matter may overwhelm macrophage function and the lymphatic system
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10 leaving deposits of material centered around the terminal bronchioles and early generation respiratory bronchioles (14) (figure 1). The
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12 particulate burden may lead to chronic focal inflammation and fibrosis, and could predispose to “scar” lung carcinoma (15) (figure 1). The
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14 efficiency of particulate clearance is a factor in how pollution affects the body.
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19 The immune and inflammatory responses to air pollutants may be genetically regulated. Many important genes involve inflammation and
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21 variation in the glutathione synthesis (16). Genetic variation in the glutathione pathway been reported to increase susceptibility to pollution-
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23 related lung function decrements in children (17). Variations in genes that control inflammatory mediators, which include toll-like receptor 4
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25 (TLR₄), tumor necrosis factor- α (TNF α), transforming growth factor- β (TGF- β ₁), and many others, have been found to increase susceptibility to
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27 the respiratory effects of pollution (16). Air pollutants affect both the innate and adaptive immune systems. Particulate matter disturbs the
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29 balance of the Th1 and Th2 leukocyte populations, resulting in dominant Th2 leukocytes, which is a feature of asthma (18).
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34 Epigenetics refers to potentially reversible modifications to DNA that control how genes are expressed, without altering the DNA sequence.
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36 Epigenetics mediate genetic and physiological responses to air pollution and are, therefore, an important cause of susceptibility to pollution-
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38 related health effects (19). Changes in micro-RNA and other RNA species also regulate gene expression, often through signaling pathways. Air
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3 pollution exposure may affect these epigenetic processes (20). Cord blood samples from several birth cohort studies, showed prenatal NO₂
4 exposure was associated with DNA methylation in several mitochondria-related genes, as well as several genes involved in antioxidant defense
5 pathways (21) Figure 2 shows different ways that air pollution can mediate tissue damage.
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10 11 12 **Air pollution and exercise** 13

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16 Physical exertion that results in increased ventilation and mouth breathing augments inhalation of air pollutants. In athletes who stress their
17 ventilatory and cardiac reserves, pollution exposure has been found to decrease exercise performance. Maximal oxygen consumption and
18 exercise duration are decreased with exposure to CO (22). Experimental exposure to O₃ reduces the exercise capacity of athletes and leads to a
19 transient decrease in spirometric function (23). Increased ambient PM₁₀ concentrations are associated with reduced marathon performance in
20 women (24). Despite these harmful effects, studies suggest that the health benefits of exercise outweigh the adverse effects of pollution
21 exposure during exercise (25) in all but the most polluted areas (26).
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31 32 **Sleep** 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47

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3 Sleep efficiency is decreased in most polluted areas, especially with increased exposure to NO₂ and PM (27). Several studies show that air
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5 pollution is associated with increased sleep apnea symptoms, possibly because of upper airway inflammation from irritant pollutants and
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7 airborne allergens (28) and household biomass smoke (29).
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12 Air pollution may affect sleep adversely in other ways. Traffic-related air pollution is highest near busy streets, which confounds sleep studies
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14 because the environment is more often noisy and illuminated. Pollution may also disturb sleep by exacerbating asthma, COPD, or other
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16 respiratory or chronic diseases. In addition, pollutants may lead to an inflammatory reaction in the central nervous system or directly interfere
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18 with neuronal function that may affect sleep (30).
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23 **Children**

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28 Children are especially harmed by air pollution for both environmental and biological reasons. Children breathe more air per unit body weight
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30 and, therefore, inhale more airborne toxicants than adults exposed to the same amount of air pollution. In many parts of the world where
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32 biomass is burned indoors for cooking and heating, small children are heavily exposed to indoor air pollution along with their mothers. Children
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34 all over the world generally spend more time outdoors and are more physically active than adults, which can result in greater exposure to
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36 outdoor air pollution.
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3 Children are biologically more susceptible to pollution because their bodies are still not mature. Lung and immune system development occurs
4 over the entire prenatal period, beginning with embryogenesis and continuing for many years after birth. Infants are born with only about 20%
5 of the alveoli that they will eventually make once they have reached adulthood. Exposures to air pollutants during the prenatal period and
6 during childhood can have harmful and irreversible effects on the lung and other organ systems.
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14 Post-natal exposures to air pollutants, including PM, O₃, and NO₂, have been associated with increased infant mortality, even in developed
15 countries, such as the United States. The strongest associations have been with post-neonatal respiratory mortality (31) (32) (33), which in part
16 may be related to respiratory infections that have links to pollution (34). Air pollution may be a “second hit” in newborns who are susceptible to
17 infection because of their immature immune systems. Post-natal diesel pollution exposure also has been found to attenuate the lung’s immune
18 response to respiratory infection and to augment the inflammatory response, which likely results in a worse course of illness (35).
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28 Air pollution has also been found to affect growth trajectories of the lung and its function during childhood, which can affect the level of
29 respiratory health achieved in adulthood. PM_{2.5} exposure has been found to impair pre- and post-natal development of tracheobronchial tree
30 (36). Many studies have found that higher exposure to PM and traffic are linked to worse lung function in childhood, and slower child lung
31 function growth (37) (38) (39), which, in turn, may limit lung function in adulthood (40). Long-term pollution exposure during childhood,
32 especially traffic-related pollution, has been associated with risk of developing childhood asthma (41) (42) and is another example of how
33 pollution exposure during childhood affects organ development and risk of subsequent chronic disease.
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Maternal-fetal health and reproductive health

Exposure to air pollution during pregnancy is associated with adverse pregnancy outcomes and reduced fetal growth. A review of more than 13,000 pregnancies in Scotland found that exposure to higher levels of PM_{2.5}, PM₁₀, and NO₂, were associated with lower infant head size during pregnancy and at birth (43). Another study across all trimesters of pregnancy showed the risk of intrauterine growth restriction was increased among women exposed to higher levels of CO, NO₂, and PM_{2.5} (44). A meta-analysis that included nearly 3 million births across 14 centers from 9 developed countries found that, after adjusting for socioeconomic status, maternal exposure to particulate air pollution was associated with a higher risk of low birth weight infants (45).

While many studies measure air pollution exposures over the entire course of pregnancy, it is thought that exposure in the first trimester of pregnancy poses a greater risk than subsequent exposures. A study of nearly 30,000 term single births in Japan found that exposure to pollutants over the course of the entire pregnancy was not associated with fetal growth restriction. However, when they examined exposures in the first trimester, O₃ exposure was associated with higher odds of small for gestational age and low birth weight infants (46). Another study of more than 5,000 mother-child pairs of the Boston Birth Cohort and found that women who were exposed to the highest levels of PM were more likely to have intrauterine inflammation (47) compared to those exposed to the lowest levels. The risk was highest for exposures measured in the first trimester of pregnancy.

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5 Air pollution increases the risk of preterm birth and low birth weight independently and additively to other known risk factors, such as lower
6 socioeconomic status, diabetes, hypertension, and smoking (48). Women who are exposed to higher levels of traffic-related air pollution during
7 pregnancy appear to be at increased risk of preeclampsia, which may be one mechanism explaining the association with preterm birth (49). Also,
8 increased exposure to O₃ and PM_{2.5} within 5 hours of delivery has been linked to higher risk of premature rupture of membranes, which
9 predisposes women to preterm delivery (50). These adverse effects on pregnancy and birth outcomes have been observed even at relatively low
10 levels of air pollution exposure. They are especially concerning because preterm birth, low birthweight and small for gestational age infants are
11 at increased risk of a variety of health problems—including reduced lung growth and cognitive problems—that can persist for their lifetimes. On
12 the other hand, reducing air pollution has prompt benefits. When measures were taken to effectively reduce air pollution during the 2008
13 Beijing Olympic Games, there was an improvement in infant birth weight in association with the reduction in NO₂, a marker of traffic-related air
14 pollution (51).
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30 **Fertility**

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34 Several studies have found that air pollution is associated with reduced fertility rates and increased risk of miscarriage. A Mongolian study found
35 a dose-dependent relationship between the monthly average SO₂, NO₂, CO, PM₁₀, and PM_{2.5} levels during pregnancy and risk of spontaneous
36 abortions (52). A few studies have shown or suggested that semen or sperm quality is decreased in areas of high pollution (53) (54).
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Vulnerable populations

Although air pollution affects people of all regions, ages, and social and economic groups, it is more likely to cause ill health and death in certain individuals. Exposures to air pollution and other environmental factors and biological susceptibility are the most important factors determining response. People living in Africa, Asia, and the Middle East on average breathe higher levels of pollutants than those in other parts of the world (1) and, therefore, sustain a greater health burden.

Both extrinsic and intrinsic factors determine vulnerability to adverse health effects from exposures to air pollution. The most important is the level of exposure. People of low social and economic status often have greater exposures to air pollution because they live in areas of greater traffic density and near point sources of pollution such as power plants and industrial facilities. Other extrinsic neighborhood factors that contribute to vulnerability include poor housing, the lack of stores to purchase healthy food (e.g., fruits and vegetables that contain antioxidants), violent crime, segregation, lack of green space, and poor access to health care (55). Poorer people are also more likely to work in dirty jobs with occupational exposures to vapors, dusts, gases, and fumes (56). Intrinsic factors that increase vulnerability to air pollution include age (very young and very old), pre-existing disease, pregnancy, genetic and epigenetic variation, smoking, and obesity (57) (58). The concept of cumulative risk combines both extrinsic and intrinsic factors when attempting to assess vulnerability of an individual or a population to the ill-effects of air pollution.

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5 When factors are combined, the effects can be additive or multiplicative. For example, pre-existing cardiopulmonary diseases and diabetes
6 increase susceptibility to the effects of particulate air pollution (58). Psychosocial stress interacts with exposure to traffic-related air pollution to
7 increase the risk of new-onset asthma in children (59) (60). It may also enhance the effects of particulate pollution on blood pressure (61). The
8 association between air pollution and cancer risk has been shown to be greater in neighborhoods with higher levels of ethnic minority
9 segregation, an indicator that may capture the cumulative impact of multiple adverse social and psychosocial exposures (62).
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19 Impoverished individuals, especially ethnic minorities, are more likely to live in segregated neighborhoods that are near sources of pollution and
20 busy roadways. Consequently, they are more often exposed to higher concentrations of outdoor air pollutants than persons with higher
21 economic status (58). They are also likely to have greater cumulative health risks from other detrimental neighborhood factors. In low-income
22 countries, women, small children, and rural residents are likely to be exposed to higher concentration of household air pollutants during cooking
23 and heating activities (63).
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32 Vulnerability is made worse by health inequality and environmental injustice (64). Proponents of environmental justice argue that investigators
33 and regulatory agencies should evaluate the cumulative impacts of environmental and social stressors in research studies and regulatory
34 policies. Pollutant and source-specific assessments of potential health risks of air pollution do not inherently reflect the multiple environmental
35 and social stressors faced by vulnerable communities that can interact to harm health. Reducing vulnerability across a population calls for
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reducing poverty, segregation, and health-damaging neighborhood environmental factors as well as reducing the ambient levels of pollutants. Strategies to achieve health equality for vulnerable communities require societal commitment of resources as well as the promulgation of air quality control measures (65).

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Table. How different types of air pollution damage tissue

Pollutant	Injury determinants	Tissue affected
Sulfur dioxide (SO ₂)	Highly soluble	Upper airway and skin damage
Nitrogen dioxide (NO ₂) Ozone (O ₃) Carbon monoxide (CO)	Less soluble (NO ₂ and O ₃ are irritating)	Deeper lung penetration Bronchial and bronchiolar injury CO: Tissue hypoxia
Particulate matter (PM ₁₀ , PM _{2.5} , PM _{0.1})	Size, structure, and composition determine toxicity	Large particles: mucous membranes, upper airways Small particles: bronchioles and alveoli Ultrafine particles: systemic tissue reactions

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3 **Legends for figures**
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8 **Figure 1. Anthracotic lung.** Inhaled particulates are usually cleared through the respiratory mucociliary apparatus and scavenged by alveolar
9 macrophages. Particles can move into the interlobular septal lymphatics and be cleared by the lymphatic system, but if these mechanisms are
10 overwhelmed, particulates may clog lymphatics and be deposited in the lung interstitium. Ultrafine particles gain entrance to mobile cells and
11 can be transported to all parts of the body. Although this anthracotic lung is characteristic of smokers and workers in dusty occupations,
12 anthracotic deposits are often found in urban dwellers from air pollution.
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21 **Figure 2. Pollution damage by systemic inflammation.** This scanning electron micrograph of the terminal and respiratory bronchioles are the
22 sites where most material accumulates making it the area of the lung most vulnerable to pollution. In addition, this figure depicts 4 ways that
23 pollution can affect all organs through systemic inflammation. Ultrafine particles pass through the alveolar-capillary membrane, are
24 endocytosed, and distributed throughout the body. They induce similar inflammatory reactions in other organs. (Copyright reserved Dean
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