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Relationship between environmental exposures in children and adult lung disease: The case for outdoor exposures

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Abstract

There is a growing understanding that chronic respiratory diseases in adults have their origins in early life. Adverse environmental exposures occurring in vulnerable periods during lung growth and development in the fetal period and in early childhood that alter lung structure and limit the growth in lung function may have lifelong consequences. Evidence is increasing that exposure to the ambient environment, including air pollutants, persistent toxic substances, water pollutants and respiratory viral infections, can inhibit lung function growth and predispose to chronic non-malignant lung diseases. These exposures generally interact with a genetic predisposition, and gene–environment interactions and epigenetic phenomena are attracting considerable study. An understanding of how ambient exposures impact on normal lung growth and development will aid in understanding of how chronic respiratory diseases of adults develop and may lead to new preventative strategies.

Keywords

Lung growth and development, antenatal exposures, air pollution, respiratory infections, arsenic, criteria pollutants

Introduction

In recent years, and despite improvements in air quality in the past decades, the role of ambient air as a major contributor to adverse human health is increasingly recognized. While air quality in many developed countries has improved, rapid urbanization and industrialization in developing countries and increasing traffic density all over the world have resulted in a lowering of air quality. Of concern, air pollution is a contributing factor to approximately 6% of the total mortality in Europe, especially air pollution associated with vehicle exhaust emissions.[1] These data are supported by a recent report showing an improvement in life expectancy when a reduction in exposure to ambient fine-particulate air pollution is attained.[2]

The concept that adult lung disease begins in childhood is being increasingly recognized. A growing body of evidence has suggested that reduced lung function in childhood and adulthood may be linked with events occurring during fetal development and post-natal life. Therefore, any factors that affect the growth and development of children's lungs can contribute to adult lung disease.[3] Both children and adults are commonly exposed to pollutants found in air, objects, food and water. Children seem to be more vulnerable and to receive a relatively higher dose than do adults in a given environment and are more vulnerable to the effects of air pollution, given that they have

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immature lung defenses against oxidant stress and immature enzymes that detoxify xenobiotics.[4,5]

Various epidemiological studies have shown an association between high levels of ambient air pollution and indices of somatic growth of the fetus, low birth weight (LBW), very low birth weight (VLBW), preterm birth, intrauterine growth restriction (IUGR), congenital defects and intrauterine and infant mortality.[6–9] In addition, ambient air pollution has been associated with decreased lung growth, asthma and increased rates of respiratory tract infections, behavioral problems and neurocognitive decrements.[10,11] Moreover, this early exposure to environmental pollutants has been associated with disease later in life.

This review focuses on the relationship between environmental exposures in children and future lung disease in adulthood. In addition, we outline the development of human lung and discuss the concept of 'windows of susceptibility' and lung growth. Furthermore, we discussed the possible modifying factors including the gene−environment interactions and socio-economic status and their relationship with lung health. We also describe health effects of major outdoor air pollutants (particulates, carbon monoxide and ozone [O_3]) and also water pollutants.

Susceptibility of the developing lung to environmental pollutants

Lung development spans from early embryogenesis to adult life, passing through several distinct developmental stages. Cellular differentiation, branching morphogenesis and overall lung growth depends on a number of different factors, including genetic and environmental ones. Exposure to toxicants during lung development has the potential to affect the overall growth and function of the respiratory system in infants and children, thus contributing to adult lung disease. Depending on the timing of exposure to all these pollutants, hazardous effects can result in significant structural and functional damage of the developing lung.[12]

The development of the lung can be divided into five developmental stages: embryonic, pseudoglandular, canalicular, saccular and alveolar. During the embryonic stage (0–7 weeks of gestation), the future lung appears around day 26 as an outgrowth of the ventral wall of the primitive foregut endoderm. These cells of the primitive foregut invade the adjacent mesenchyme. The tracheal bud rapidly divides into two branches that develop into the two main bronchi. Furthermore, they continue a series of processes (growth and branching morphogenesis) to form the highly complex structures of the airway tree. Simultaneously, during this phase of lung development, pulmonary arteries will branch off the aortic arches to form a vascular plexus near the mesenchyme. The embryonic stage is followed by the pseudoglandular stage (7–17 weeks gestation), in which branching of the airways down to the terminal bronchiole continues. During this stage, capillaries are distributed in the mesenchyme and will grow according to the same pattern as the airways. The cannalicular phase (17–27 weeks gestation) is characterized by the formation of respiratory bronchioles, alveolar ducts and primitive alveoli. During the saccular phase (27–36 weeks gestation), the peripheral airways enlarge and the gas-exchanging surface area increases as the airway walls thin. The alveolar stage (36 weeks gestation-10 years post-natal age) is the longest phase as it continues through childhood into adolescence. This phase consists of the formation of the alveolar gas exchange area. Alveolar multiplication continues after birth, being most rapid during the first 18–24 months of age[13,14] and possibly being completed by 8–10 years of age.[15]

The development of the complex architecture and its function is controlled by numerous factors, including growth factors, transcription factors, extracellular matrix molecules, integrins and intercellular adhesion molecules. Cell proliferation and apoptosis also occurs in combination throughout lung development and growth. As mentioned before and given that this process of lung development begins early in embryogenesis and continues well after birth, factors that interfere with the developmental program–morphogenesis, cellular differentiation and proliferations, alveolarization and maturation of the pulmonary immune, vascular and neural system–may result in abnormal lung growth, reduced lung function and risk of disease in later life.[7,12,16] This could explain why exposure to environmental pollutants is likely to have different consequences in the adult with that found in children. Exposure to substances during specific periods or 'windows of susceptibility' of development can adversely affect the lungs and airways and have lifelong consequences. Similar exposures occurring at other less vulnerable times, for example, during adulthood may be innocuous; that is, it is the developmental timing of an exposure that largely determines the outcome.

Numerous studies have shown that lungs are extremely sensitive to a large number of inhaled

toxicants; thus early and lifetime exposure to environmental pollution can be detrimental. Early life exposures may predispose the developing fetus,[7,17] infants,[9] children,[18,19] adolescents[10] and adults[2,20] to a variety of respiratory conditions. Moreover, there are several factors including the increased vulnerability of children, unique exposure pathways for the fetus, infant and child, dynamic physiological maturity, gene−environmental interactions and social factors that could result in different individual susceptibility and different outcomes in individual children.[5,21]

Modifying factors

Age and physiological development

The hazardous effect of environmental pollution begins very early in life. As discussed above, exposure to high levels of air pollution during pregnancy may have adverse consequences in the developing fetus. Toxicants a pregnant mother is exposed to can enter the fetal circulation through the placenta and have a significant impact on the growth and development of the baby and increase perinatal morbidity and mortality.[6,9,11,17,22] Maternal exposure to SO_2 during pregnancy increases the risk of LBW and VLBW.[8,11] The effect of pollutant exposure varies with the gestational timing of the exposure. Liu and colleagues[8] reported that exposure to relatively low concentrations of SO_2 and CO during different stages of pregnancy was associated with adverse effects on birth outcomes. Exposure to SO_2 during the last month of pregnancy was associated with preterm birth, whereas exposure during the first month of pregnancy was associated with IUGR. Preterm birth was also associated with exposure to ambient CO, probably from motor vehicle exhaust (OR = 1.08, 95% CI, 1.01–1.15, for a 1.0 ppm increase) during the last month of pregnancy.[8]

Fetal exposure to tobacco products also has important detrimental effects on the developing baby, including LBW, preterm birth, placenta previa and perinatal mortality.[11] In addition, maternal smoking has been shown to have important long-term effects on children's respiratory health. Women who smoke during pregnancy are likely to continue to smoke after birth;[23] therefore it has been difficult to differentiate the effects of in utero exposure to smoking from post-natal exposure to environmental tobacco smoke (ETS). Nevertheless, a substantial number of studies have shown that both ETS and in utero exposure to maternal smoking are important risk factors for respiratory infections, decreases lung growth, increases both the prevalence and severity of asthma.[23–26] Numerous studies have shown that in utero exposure is associated with significant reduction in lung growth and deficits in lung function at birth, which will persist into adulthood.[27–29] In a study performed in 12 southern California communities, Gilliland et al.[30] studied the effects of maternal smoking during pregnancy and childhood ETS exposure on asthma and wheezing in 5672 school-age children. In utero exposure without subsequent ETS exposure was associated with increased prevalence of physician-diagnosed asthma, persistent asthma symptoms, need for asthma medication in the last 12 months, wheezing with exercise and emergency visits because of acute episodes of wheeze.

Both antenatal and post-natal exposure to ambient air pollutants have been associated with deleterious effects, including decreased lung growth, increase in the rates of and severity of respiratory tract infections, behavioral problems, neurocognitive decrements and mortality from all causes, respiratory causes and from lower respiratory infections/pneumonia.[31] An increased prevalence of sudden infant death syndrome has been found in association with increased levels of air pollutants, specifically SO_2 and NO_2.[32] In addition, a previous meta-analysis reported that an increase in 10 $\mu g/m^3$ in particulate matter (PM) of <10 μm (PM_{10}) was associated with 5% increase in post-neonatal mortality for all causes and around 22% for post-neonatal mortality for respiratory diseases.[33]

Infants and children have been shown to be extremely susceptible to the effects of environmental pollutants.[5,7,9,21,34] The increased susceptibility comes from the dynamic developmental physiology of children which increases the relative dose and the prolonged period of post-natal maturation of the respiratory, immune and central nervous systems that increase the 'windows of susceptibility' for these organs.[4,35,36] Relative to body size, children breathe more air, drink more water and eat more food than adults do.[35] In addition, older children tend to spend more time outside than adults, particularly during summertime and late afternoon thus increasing exposure to ambient air pollutants.

Several epidemiological studies have reported adverse effects on lung development in children, leading to decreased lung function as children reach

adulthood.[16,19] In the Californian Children's Health Study, Gauderman and colleagues[10] followed up 1759 children aged 10-18 years in 12 southern California communities. Over a period of 8 years, the authors found a significant association between deficits in the growth of forced expiratory volume in 1 second (FEV_1) and exposure to NO_2 ($p = .005$), acid vapor ($p = .004$), PM with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) and elemental carbon ($p = .007$). The estimated proportion of 18-year-old individuals with a low FEV_1 (less than 80% predicted) was nearly five times larger in the most polluted communities (highest level of exposure to $PM_{2.5}$). Furthermore, in an analysis of a subset of these children who moved away from the study area to areas of lower ambient pollution, Avol et al.[37] observed an improvement in lung function growth, suggesting that some of the effects of pollution may be reversible in the absence of the offending pollutant. Moreover, in the same prospective longitudinal study, Gauderman et al.[38] found a direct association between residential exposure to traffic and the 8-year lung function growth. Children who lived within 500 m of a freeway had substantial deficits in the 8-year growth of FEV_1 and maximum mid-expiratory flow (MMEF), compared with children who lived at least 1500 m from a freeway.

Epidemiological studies have shown that deficits in airway function present shortly after birth or in early childhood may predict airflow limitation in adulthood.[39–43] Data from the Melbourne Asthma Study revealed that loss of lung function in children with asthma occurs early and remains constant throughout adolescence and early adult life.[44] During this study, a group of children with a past history of wheezing was randomly selected from the Melbourne community at the age of 7 years (during 1969), and a further group of children with severe wheezing was selected from the same birth cohort at the age of 10 years. These individuals have been followed prospectively at 7-year intervals, with the last review in 1999, when they were approximately 42 years old. Throughout those years, children classified as having either mild or severe asthma had consistently lower lung function (FEV_1/FVC ratios) than those without asthma. Moreover, these lower lung function levels were already established during childhood, with no further deficits occurring throughout adulthood up to the age of 42 years. Similar data are available from other longitudinal birth cohort studies.[42,45] Thus lung function growth in childhood is one determinant of lung function in adulthood, thus having a lifelong effect on respiratory disease risk.[12]

Early childhood infections

Upper and lower respiratory viral infections are closely associated with wheezing and exacerbations of asthma throughout life. Recurrent episodes of wheezing, especially with respiratory viral infections have been associated with asthma in childhood and adulthood, and chronic obstructive lung disease in adults. Specific pathogens most commonly involved are respiratory syncytial virus (RSV), rhinoviruses (RV), parainfluenza viruses, metapneumovirus, and influenza viruses. This relationship is not completely understood, however, some authors have suggested that during early life, exposure to acute viral infections can lead to persistent alterations in immune responses and airway function in susceptible individuals.[46] Furthermore, acute lung injury secondary to viral infections may alter lung growth with further deficits in lung function.[47] Children participating in the Tucson children's respiratory study, who had RSV lower respiratory illness (LRI) in the first 3 years of life had lower baseline lung function when asymptomatic in early adolescence that 'corrected' following inhalation of bronchodilator.[47] These data were interpreted as the RSV infection altering the baseline vagal tone of the airway smooth muscle. Damage to the epithelium, increased mucus production, inflammatory and antiviral responses such as release of nitric oxide (NO), cytokines and chemokines are some of the effects of the viral infection and immune response to this infection. In addition, viral infections will generate factors that are likely to influence lung development and airway remodeling, including vascular endothelial growth factor, NO, transforming growth factor (TGF-α and β) and fibroblast growth factor.[48] The importance of RV as a lower airway pathogen and as a cause of early childhood wheeze is becoming increasingly recognized.[49–51] However, the contribution of RV LRI in early life to adult obstructive lung diseases remains to be clarified. Holt and Sly[52] have recently postulated that these early life infections may indeed predispose to the subsequent development of COPD in adults as part of a continuum from atopic asthma, non-atopic asthma to COPD.

Gene–environment interactions

Despite the potential deleterious effects of environmental pollution in the population as a whole, there

is growing evidence to suggest individual susceptibility to adverse health effects of environmental toxicants. Genetic variation between individuals has the potential to affect lung development, lung maturation and lung injury and repair, thus affecting lung health in adults.[53] Variations in genes related to detoxification of xenobiotics, especially those involved in antioxidant defense in the lungs have attracted considerable attention. Oxidative stress resulting from exposure to major air pollutants, especially traffic-related pollutants including particulate matter, O_3 and NO_2 is involved in decrements of lung function and lung function growth.[54] Individuals with reduced antioxidant defense capability appear to be more vulnerable to these exposures.[55-57] A complete review in oxidative injury and pathogenesis of lung disease is beyond the scope of this review and can be found elsewhere.[54]

Oxidative stress in the lung can result in tissue damage through a variety of mechanisms, including lipid peroxidation. To cope with living in an oxidant environment, the lung has developed multiple antioxidant defenses, including the superfamily of glutathione S-transferases (GSTs). When the production of reactive oxygen species (ROS) overwhelms the antioxidant system, significant lung damage occurs. GST enzymes catalyze the conjugation of toxic molecules with the reduced form of glutathione (GSH) and 'neutralizing' ROS. Variations in the genes coding for this superfamily of enzymes may result in loss of enzyme function, including complete loss with 'null' mutations. Polymorphisms in the GST classes (GSTM, GSTT and GSTP) have been associated with specific effects on protein expression or function.[55–57] A significant number of genetic linkage studies come from southern California. Gilliland et al.[56] reported a significant relationship between GST genotypes and acute respiratory illness in children. They observed that children who were homozygous for GSTP1 Val105 variant allele had lower incidence rates of upper and lower respiratory infection than those children who were homozygous for the Val105 allele. Furthermore, they found that children who were homozygous for the GSTP1 val105 allele had slower lung function growth than children with one or more ile105 alleles. In addition, children with asthma, who were homozygous for the GSTP1 val105 allele, had substantial deficits in FVC, FEV_1 and MMEF compared to children without asthma.[55] In further analysis, Breton et al.[58] recently reported the effects of variants in GST genes on lung function in 2108 children from this cohort. Variation in the GST μ family locus was associated with lower FEV_1 and MMEF. At the same time, they found a significant relationship between lower lung function growth in children of mothers who smoked during pregnancy and had variation GSTM2. Moreover, in a subgroup of the same prospective longitudinal study, Islam and colleagues[59] studied the association between GSTs, exercise, O_3 exposure and asthma in school children. They found that functional variants of both GSTP1 and GSTM1 were associated with new onset asthma during adolescence. However, there was a protection effect of the val105 variant allele and onset of asthma in this group of children, especially those living in areas with high O_3 exposure. Other genetic association studies have shown that polymorphisms in the gene for tumor necrosis factor α (TNF-α)–a proinflammatory cytokine–was associated with decreased lung function after exposure to O_3.[53]

Nutrition

Dietary factors and nutritional status play an important role in the respiratory health of an individual.[60–63] Nutritional status during fetal and infant development is particularly important. Maternal ill health during pregnancy and other factors associated with reduction in the supply of nutrients to the developing fetus have been associated with IUGR, and increased post-natal respiratory morbidity and mortality.[7] A diet rich in antioxidant vitamins and the 'Mediterranean' diet have been associated with improved respiratory health, especially in children.[62] Epidemiological studies have associated regular intake of fruits and vegetables high in carotenoids and vitamins with greater lung function and decreased incidence of asthma.[60–62] One potential mechanism for this effect is via boosting the lungs' antioxidant defenses, although direct data to confirm this are lacking. Dietary supplementation with omega-3 fatty acid and vitamin E during pregnancy has been claimed to reduce the incidence of atopy in children;[62] however, again mechanistic data are lacking. However, a deficient diet has been associated with an increase in susceptibility to adverse environmental toxicants such as tobacco smoke, air pollution (O_3, NO_2, PM) and allergens.[61,62]

Socioeconomic status

Socioeconomic status (SES), whether measured by education, income wealth, employment type/status, other indices of social class or by a combination of variables has long been known to be associated with

adverse health outcomes. Demographic factors such as race/ethnicity, gender, urban/rural place of residence and geography can modify the relationship between SES and health. A growing body of research suggests a relationship between social disadvantages in early life and adverse health outcomes.[64–66] Poor housing associated with disadvantaged social status, including factors such as home dampness, increased house dust mites and unventilated gas stove usage may contribute to higher morbidity and mortality from a broad range of conditions in both children and adults, especially respiratory conditions. The effect of SES on asthma is likely to be multi-factorial and include adverse environmental exposures; poor access to health care; exposure to family and financial stress, domestic and community violence, and racial segregation and psychological/cultural factors.[66,67] The SES of a child's family in early life has been associated with pulmonary function in later life.[64,68] Lawlor et al.[64] reported that childhood poverty was associated with a decrease in FEV_1, FVC and FEF_{25-75} later in life. Hancox and colleagues[69] studied the relationship between SES and asthma in a longitudinal cohort of nearly 1000 individuals in New Zealand followed up from birth up to the age of 26 years. There was no association between current asthma, wheeze or bronchodilator response and SES in early adulthood. The FEV_1/FVC ratio was lower in those with lower educational achievement and lower SES, but this relationship did not reach statistical significance. In addition, they found no convincing evidence of an association between SES during childhood and asthma at any age. Consistent with other available evidence, they found a significant trend to increased atopy with higher childhood SES. Children from low income families participating in a longitudinal birth cohort in Perth, Australia, were more likely to have asthma in childhood and adolescence.[70] However, these relationships were complex, stronger in girls than in boys and related to chronic low income throughout childhood rather than low income in early life.[70]

Specific examples of outdoor pollution

Exposure to ambient air pollution and to specific pollutants has been associated with a variety of adverse health outcomes, including congenital abnormalities; abnormal fetal growth, for example, altered somatic growth, IUGR, LBW and premature birth; and increased perinatal mortality and infant death.[6,7,11] Outdoor pollution includes a variety of substances (particulates and air toxicants) that vary with the source and in significant concentrations can affect humans, animals, vegetation and the environment. The Environmental Protection Agency (EPA) of the United States sets standards and regulates six 'criteria' pollutants, that is: particle pollution (often referred to as PM and referred to by particle size), ground-level O_3, CO, sulfur oxides (especially SO_2), nitrogen oxides (especially NO_2) and lead. Of the six pollutants, particle pollution and ground-level O_3 pose the most widespread health threats. The EPA regulates these pollutants by developing human health-based and/or environmentally based criteria (science-based guidelines) for setting permissible levels. However, other toxicants may contaminate ambient air and compromise respiratory health via inhalation exposure, including pesticides, persistent organic pollutants (POPs) and heavy metals. Ma et al.[71] recently reported an increase in hospitalizations for asthma and respiratory infectious diseases in children living in the vicinity of hazardous waste site that contained POPs. The association was strongest for residents in the lowest quartile of median family income. The most reasonable explanation for these data is that volatilizing of waste results in contamination of air with resulting inhalation exposure of children living nearby.

Common sources of ambient air pollutants include mobile (e.g. traffic-related) and fixed (e.g. industrial) sources. Most emissions result from the incomplete combustion of fossil fuels. O_3 is a secondary pollutant formed in the environment from the photochemical reaction (i.e. in the presence of sunlight) between hydrocarbons and NO_2. Natural sources of emissions, including volcanoes, forest fires and dust storms, may contribute to ambient air pollution in some parts of the world. Table 1 summarizes individual pollutants, sources and health effects. However, exposure to a mixture of pollutants is the norm and quantifying the health effects of exposure to mixtures can be problematic.

Exposure to pollution mixtures can vary by location, proximity to roads, proximity to industrial area, seasonality, time of day and meteorological factors. Traffic-related pollution consists of a complex concentration of fine and ultrafine particles with higher concentrations of CO and NO_2 emissions from gasoline and diesel engines, together with dust from wear of road surfaces, tires and brakes. Traffic emissions remain a major source of air pollution in urban areas,

Table 1. Sources and main effects of individual components of ambient air pollution

Type	Source	Main health effect
Ozone ($O_{3)}$	Photochemical reactions involving ultraviolet radiations on environmental mixtures of NO_2 and hydrocarbons emitted from vehicle emissions	Bronchial hyper-responsiveness; lung function reduction; increased prevalence of respiratory symptoms; increased hospitalization rate for respiratory disease; reduced exercise tolerance
Particulate matter	Mixture of solid and liquid particles from different sources Natural sources: volcanoes; sea spray; pollens; fungal spores; soil particles Man-made particles: vehicle traffic (friction on road surfaces); industrial processes; construction work	Irritates nose and throat; exacerbation of allergies; lung function reduction; increased prevalence of cough and wheeze; increased mortality from cardiovascular diseases; increase in asthma exacerbations
Sulfur dioxide	Fuel combustion; vehicle traffic	Lung function reduction; Increase in the prevalence of respiratory symptoms; increased mortality from respiratory disease
NO_2	Precursor of photochemical smog; gas combustion (gas cooking/kerosene heaters); automobile exhaust; power plants; other sources that burn fossil fuels	Bronchial hyper-responsiveness; lung function reduction; increased respiratory symptoms; reduced exercise tolerance
Carbon monoxide	Fuel combustion	Reduced exercise tolerance

NO_2 = nitrogen dioxide.

thus a main contributor to air pollution and related lung injury. Several studies have found a significant association between exposure to traffic-related emissions and higher rates of adverse respiratory health outcomes, such as lower lung function, an increased incidence of respiratory symptoms and an increase in the incidence of allergic diseases in both children and adults.[72-76] Exposure to traffic-related air pollution, in particular diesel-exhaust particles, may lead to reduced lung function in children living near major motorways. Gauderman et al.[38] showed that local exposure to major traffic adversely affected lung function growth in a group of children who were prospectively followed up for a period of 8 years. Children living within 500 m from a freeway in southern California had substantial deficit in FEV_1 growth compared with children who lived at least 1500 m from a freeway.

In addition to traffic-related sources, incomplete combustion of fossils fuels (oil and coal) in power plants, factories, office buildings and homes and by the incineration of garbage may contribute to ambient air pollution. Different types of industry may emit different pollutants and these different sources may have differing impacts on respiratory health. Petroleum refineries emit volatile organic compounds (VOCs), hydrocarbons and particulates. Children living near the petrochemical pole of La Plata, Argentina, had lower lung function and worse respiratory health than children living in areas with heavy traffic-related pollution or in relatively unpolluted areas of the city.[75] Several studies have demonstrated that living in areas near a chemical factory can also have negative effects on respiratory health. Jang and colleagues,[77] studied the association between living near a chemical factory and airway hyper-responsiveness in a cross-sectional study involving 670 children living in three cities in southeast Korea. Children aged 10–13 years of age underwent spirometry, allergic skin tests and methacholine challenge (PC20 was used as the index of airway hyper-responsiveness). There was a statistically significant increase in AHR in children living near the chemical factory compared to those living in a less polluted area. Atopy also was significantly more prevalent near the chemical factory when compared to coastal or rural areas (35% vs 27.3% and 23.3%, respectively, $p < .007$).

Ozone

O_3 is generated at ground level by the action of sunlight (ultraviolet radiation) on nitrogen oxides and reactive hydrocarbons derived from vehicle emissions (photochemical reaction). Because O_3 trends depend not only on substrate supply (NO_2 emitted by vehicles) but also on the intensity of sunlight and temperature, peak O_3 concentrations occur most frequently during summer months and in the afternoon. Epidemiological studies have provided evidence that

high-ambient O_3 concentrations are associated with an increased rate in hospital admissions and emergency department visits for respiratory disease such as asthma attacks.[78,79] Furthermore, O_3 has been associated with decrease in exercise tolerance in athletic performance, increase in respiratory tract infections and decrements in lung function.[7,10,80–82] Children who engage in physical activity outdoors, especially during summer time and holidays, may be at higher risk for the adverse health effects of O_3.[18] Kopp et al.[83] showed that O_3 exposure was associated with a significantly lower FVC and FEV_1 in children exposed to high ambient O_3 concentration during the summer season but not during winter months. In addition, Ihorst et al.[84] demonstrated that medium- to long-term exposure to lower ambient O_3 levels was associated with greater growth in lung function. Long-term exposure to high ambient O_3 has been investigated in several studies. Galizia and Kinney[81] observed significantly lower lung function and increase in respiratory symptoms such as cough, increase in phlegm and wheeze apart from colds in a group of college students who never smoked and lived in residence areas of high O_3 exposure for four or more years.

Biological plausibility for the effects of O_3 exposure on lung growth and development comes from a series of elegant studies performed on infant rhesus monkeys. Monkeys exposed repeatedly to O_3 throughout infancy developed shorter, narrower peripheral airways with alveoli arising more proximally from the bronchial tree.[85] These changes would be expected to increase airway responsiveness and to predispose to more respiratory disease if similar changes occur in exposed human infants.

Particulate matter

PM refers to a mixture of solid and liquid particles suspended in air. These particles may have different origins, can vary in size and composition; they generally have a carbonaceous core with various chemicals adsorbed to their surface. PM also includes gaseous pollutants, sulfate and nitrate ions, acid condensates, soil and road dust, soot, ash, molds and pollens. PM is commonly categorized based on size and grouped according to aerodynamic diameter. PM_{10}, that is, particles with an aerodynamic diameter of <10 μm can reach the lower airway but not the gas-exchange region. $PM_{2.5}$ (<2.5 μm aerodynamic diameter) are referred to as respirable particles and can gain access into the gas-exchange region of the lung. Ultrafine particles (<0.1 μm aerodynamic diameter) and nanoparticles (<100 nm in diameter) are also found in ambient air, especially in traffic-related pollution. Common sources of PM are factory smoke stacks, power plants, mining and construction activity, agricultural activity, vehicular exhaust and combustion of wood and other materials. Natural sources include volcanoes, sea spray, pollens, fungal spores and soil particles.

Many studies have shown a strong association between short-term and long-term exposure to PM and several adverse health effects in both children and adults, including increased mortality from respiratory and cardiovascular diseases, exacerbation of allergies, asthma, chronic bronchitis, increase in respiratory infections, decrement in pulmonary function and other adverse effects.[86–90] Several epidemiological studies have linked high levels of PM exposure during pregnancy and adverse events such as low birth weight, IUGR, preterm birth and infant respiratory-related mortality.[11,22] Schwartz[90] found a statistically significant negative correlation between total suspended particles and lung function among children and adults between 6 and 24 years of age, participating in the National Health and Survey Study II in the United States. The prospective study performed by Gauderman and colleagues[10] in children living in southern California communities, reported lower rates of annual lung function growth in children living in areas of high PM_{10} and inorganic acid vapor assessed over a 8-year period. A subgroup of this population (110 children) who had moved from the original communities participating in the study were analysed to determine whether changes in air quality caused by relocation were associated with changes in annual lung function growth rates. They demonstrated that children who moved to areas of higher PM_{10} than the study area had lower rates of annual lung function growth, whereas children who moved to areas of lower PM_{10} levels showed increased growth in lung function.[37] Similar data are available from other studies with improvements in air quality being associated with a reduction in respiratory symptoms,[91] a decreased rate in the age-related decline[92] in FEV_1 and an improvement in life expectancy in the United States.[2]

Diesel-powered cars are being promoted as being more environmental friendly, as they produce up to 25% less CO_2 than petrol-powered engines. However, diesel exhaust particles are thought to pose a particular threat to respiratory health. Acute and chronic

exposure to diesel exhaust causes irritation of nose and eyes, increased inflammatory responses within the airways, increased sputum production, increased cough and lung function decrements.[72,93]

Nitrogen dioxide (NO_2)

NO_2 is generated primarily by fossil fuel combustion and found in outdoor air in urban and industrial regions. NO_2 participates in the photochemical reaction, in conjunction with ultraviolet radiation from sunlight and hydrocarbons, which results in the production of O_3. The main sources of NO_2 include vehicle exhaust, power plants and other sources that burn fossil fuels. NO_2 has been associated with adverse respiratory health effects, probably through inflammation as it is an oxidant pollutant. In some observational and epidemiological studies, NO_2 has been associated with increase in the incidence of asthma, increase in asthma-related symptoms and reduced lung function in children.[94,95] Hernandez-Cadena and colleagues[96] reported a reduced response to short-acting beta agonists (SABA), as judged by FEV_1 response, in children exposed to higher levels of NO_2. These interesting data require confirmation in a more comprehensive longitudinal study.

Sulfur dioxide (SO_2)

SO_2 is a colorless gas that is produced from the burning of fossils fuels (e.g. coal and petroleum refining) and is a component of traffic-related pollution. Erupting volcanoes are a natural source of SO_2. In addition, when SO_2 combines with water, it produces sulfuric acid, which is the main component of acid rain. SO_2 has clearly been shown to be harmful in humans and animals and is associated with decreased lung function and increase in respiratory symptoms, including dyspnea, cough and wheeze in asthmatic individuals. In addition, SO_2 has also been associated with adverse cardiovascular effects.[86]

Water pollution

Arsenic

Arsenic is a poisonous metalloid that occurs naturally as well as being used in agriculture as pesticides, herbicides and insecticides and in mining for extraction of precious metals. Arsenic exposure to humans mainly occurs from the ingestion of arsenic-contaminated water and food, but humans can be exposed also from air contamination. Major arsenic toxicities have been reported in areas of India, Bangladesh, Taiwan and other Asian countries and also in the Western World in countries such as Mexico, United States, Argentina and Chile. Arsenic is classified as a human carcinogen and is associated with cancer of various organs. Chronic exposure causes skin lesions (pigmentation changes and keratosis), hypertension, diabetes mellitus, neurologic, cardiovascular and respiratory complications. Skin abnormalities have long been known to be hallmark signs of chronic arsenic exposure in adults.

Arsenic is unusual in that exposure via ingestion is associated with lung disease. Non-malignant lung disease associated with arsenic ingestion was first reported in Chile in early 1970s. Autopsies on five children with clinical manifestations of chronic arsenic toxicity showed abnormal lung tissue, and two having characteristics of interstitial lung disease with mild bronchiectasis.[97] A large cross-sectional epidemiological survey was performed in West Bengal, where data from 6864 non-smoker participants of all ages who lived in an arsenic-affected region were analysed. In participants with arsenic-associated skin lesions, the age-adjusted prevalence odds ratio estimates for cough, crepitations and shortness of breath for females were 7.8, 9.6 and 23.2 and for males 5, 6.9 and 3.7, respectively.[98] To establish the risk of bronchiectasis in persons with arsenic-caused skin lesions, Mazumder and colleagues[98] recruited 108 participants with skin lesions and 150 participants with no skin lesions from a population survey in an arsenic-exposed region in West Bengal, India. Participants with a 2-year history of chronic cough ($N = 38$) underwent high-resolution CT scan. CT evidence of bronchiectasis was found in 18 (67%) participants with skin lesions and 3 (27%) subjects without skin lesions. Overall, subjects with arsenic-caused skin lesions had a 10-fold increased prevalence of bronchiectasis compared with subjects who did not have skin lesions.[98] Furthermore, in the same area, another study using a cohort of 287 participants who were exposed to 500 μgL^{-1} of arsenic, levels well above the current World Health Organization recommended maximum of 10 μgL^{-1}, reported a significant association between skin lesions and reduced lung function.[99] There is a growing body of evidence that shows that ingestion of arsenic through drinking contaminated water leads to significant chronic non-malignant lung disease including obstructive and restrictive lung disease and bronchiectasis.[100]

In utero arsenic exposure via drinking water has been shown in a number of studies to have an influence on health outcomes. Arsenic is a potent teratogen that is capable of crossing the placenta[101] and has been linked to fetal loss during pregnancy and increases in the frequency of birth malformations.[102] Again, the bulk of research on in utero exposure to arsenic via drinking water has focused on malignant outcomes with little study on the non-malignant respiratory effects of such exposure. Recent, data from an unfortunate natural experiment in the Antofagasta region of Chile have demonstrated the potential effect of early-life aresenic exposure on long-term non-malignant respiratory disease.[103] In the late 1950s, a new source of water was tapped in order to supply drinking water to Antofagasta. This water source was used for over 20 years before it was realized that it contained excessive levels of arsenic (approaching 1000 μgL^{-1}) and a treatment plant was installed.[103] The nature of this exposure event means that the effect of high levels of arsenic in drinking water on health outcomes can be studied at discrete life stages. Smith et al.[103] demonstrated an increase in mortality due to obstructive lung disease (primarily in the form of bronchiectasis) in later life in people exposed to arsenic in early life during this exposure event. Interestingly, while the standardized mortality rate (SMR) for bronchiectasis was elevated in those people exposed post-natally in early life (SMR: 12.4, 95% CI [3.3–31.7]), the risk of death due to obstructive lung disease was even greater in those who were exposed during this event in utero (SMR: 46.2, 95% CI [21.1–87.7]).

Conclusion

The prevalence of chronic respiratory diseases such as asthma and chronic bronchitis has increased in both children and adults. Changes in genetic predisposition, way of living and changes in environmental factors may explain in part this increase. Exposure to environmental pollution at different stages of development has shown to be an important risk factor for lung disease and allergies later in life. There is growing evidence that support that several chronic lung diseases in adulthood have their etiology in infants, children and even during prenatal development; probably attribute to an increase in vulnerability of the lungs to the detrimental effects of pollution during these developmental phases. Understanding the complex process of lung development may help in determining the critical windows of susceptibility during pre- and post-natal lung growth. Knowledge about different modifying factors that could influence the susceptibility of the developing lung to the different environmental toxicants is important especially when to identify population at risk. Growing evidence links both prenatal maternal exposure and post-natal (infants, children and adolescents) exposure to O_3, NO_2, SO_2 and PM with decreased lung growth, increased rates of respiratory tract infections, increase in the risk of respiratory allergic diseases and other harmful effects including death. Understanding the process by which these environmental pollutants induce oxidative stress, which at the end leads to significant inflammation and lung disease is crucial as this process can be ameliorated by antioxidant treatment.

There is urgent need for public health interventions to improve air quality and therefore, improve health outcomes in the population. Health professionals must advocate clean air strategies, especially those with political decision power. Further research in this area is highly relevant from both a public health and clinical point of view. Moreover, epidemiological studies incorporating new technological advances in evaluating exposure assessment and susceptibility factors in specific individuals are required.

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