Impact of Environmental Conditions on the Respiratory System

A Pulmonary Physiology Perspective

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Introduction

According to the World Health Organization (WHO), approximately 7 million people die annually because of exposure to air pollution.

The relationships between climatic conditions, air quality, pollution, and public health parameters are complex and multidimensional. Despite localized efforts to reduce environmental exposure, tobacco smoking and air pollution remain urgent public health challenges that contribute to the increasing prevalence of respiratory diseases.

Environmental conditions such as air pollution, heat, and extreme cold have significant impacts on the respiratory system. Barrier systems, such as the respiratory system, are directly affected by these factors.

In this case, many environmental stressors exert similar actions on respiratory physiology and therefore share pathophysiological mechanisms in altering pulmonary pathology. In general, we will examine how inhaled antigens generate oxidative stress and a local proinflammatory environment, leading to epithelial destruction and distortion of the lung parenchyma by ineffective repair mechanisms. Finally, the airway caliber, resistance, conductance, lung volume, and alveolar-capillary gas exchange are evaluated.

The aim of this chapter is to review the impact of environmental conditions on lung function. The basic concepts of pulmonary physiology should be reviewed in other chapters of this book.

Mechanisms of Environmental Impact on Pulmonary Physiology

The susceptibility of the respiratory system to environmental pollutants is primarily attributed to its extensive surface area and role as a barrier to the external environment.
The characteristics of the inhaled pollutants significantly influence their deposition, retention, and overall impact on the respiratory system.

The key determinants of particulate matter deposition in airways include size, shape, and solubility. Particles with lower densities and molar masses exhibited a greater diffusion capacity, enabling them to reach the lower airways. Highly soluble contaminants tend to deposit in the upper airway through interactions with respiratory mucous secretions, whereas contaminants with low solubility possess an enhanced ability to traverse the tracheobronchial tree. Owing to their inability to penetrate the alveolocapillary membrane, these contaminants may be retained for extended periods, potentially lasting several months.

The site of deposition within the tracheobronchial tree elicits relatively specific symptoms: deposition in the upper airway induces local inflammation, manifesting as rhinitis, pharyngitis, or laryngitis; in the transitional airway, it results in obstructive symptoms due to inflammation, such as bronchitis, and inflammation of the lung parenchyma, leading to more severe symptoms, including pulmonary edema, pneumonia, or fibrosis.

Regardless of etiology, environmental insults share a series of pathophysiological mechanisms that induce cellular and molecular changes that affect essential functions.

- **Oxidative stress and inflammation**

  Reactive oxygen species (ROS) initiate signaling cascades that are crucial for metabolic regulation and stress responses. These cascades are subsequently modulated by regulatory pathways, which include enzymatic systems responsible for scavenging both intra- and extracellular oxygen free radicals.

  Environmental exposure can compromise anti-inflammatory defense mechanisms such as NRF2 and KEAP1 by inducing conformational changes in proteins involved in metabolism, excretion, iron regulation, autophagy, proteasome function, DNA repair, and fatty acid oxidation. Ultimately, the persistent induction of proinflammatory states leads to apoptosis and necrosis. These inflammatory

conditions contribute to the deterioration of the functional lung epithelium and the progression of chronic lung disease.

- **DNA damage**

- **Epigenetic instability**

Epigenetic changes are defined as heritable modifications in gene expression that occur without alterations in the DNA sequence.

Prolonged exposure to environmental pollutants has been linked to epigenetic modifications over time, particularly DNA methylation, which is associated with genomic aging. Consequently, chronic exposure to pollution has been proposed to accelerate the epigenetic clock.

- **Mitochondrial dysfunction**

The mitochondrion is responsible for managing the cellular energy necessary for essential functions, and its performance is influenced by exposure to environmental pollutants.

Alterations in mitochondrial DNA (mtDNA) content are indicators of mitochondrial damage and function. The significance of mitochondrial toxicity as a consequence of environmental pollutants lies in its crucial role in regulating the oxidative stress induced by such exposure.

- **Endocrine dysfunction**

The endocrine system can be effectively categorized into the sex hormone axis, adrenal axis, and growth hormones/insulin-like growth factors (IGLF). Endocrine-disrupting chemicals (EDCs) are substances capable of interfering with hormonal action. Through these functional modifications, EDCs alter intercellular communication by modifying signaling factors such as interleukins, chemokines, and growth factors, as well as protease secretion, extracellular vesicle transport, and components of the extracellular matrix.

Exposure to environmental pollutants has been demonstrated to dysregulate epidermal growth factor in the lungs, accompanied by increased levels of serum proinflammatory modulators.

- **Alteration of the microbiota**

The microbiota present in organs with barrier functions, such as the respiratory system, along with modulation of the immune system, are critical components in the interaction between environmental pollution and pulmonary physiology. These factors are indicative of the development of lung diseases including childhood asthma and allergies.

Exposure to environmental pollutants and the presence of pathogens elevate the likelihood of obstructive pathologies due to bronchial hyperreactivity, which is mediated by T cell activation and a reduction in the antimicrobial response. For instance, the extent of environmental contamination has been shown to contribute to the severity of COVID-19, as evidenced by the prolonged need for ventilatory support.

- **Central nervous system dysfunction**

Air pollution is associated with receptor-mediated dysfunction of the autonomic nervous system within the tracheobronchial tree. This effect may lead to systemic translocation, potentially involving the migration from the olfactory nerve to the central nervous system.

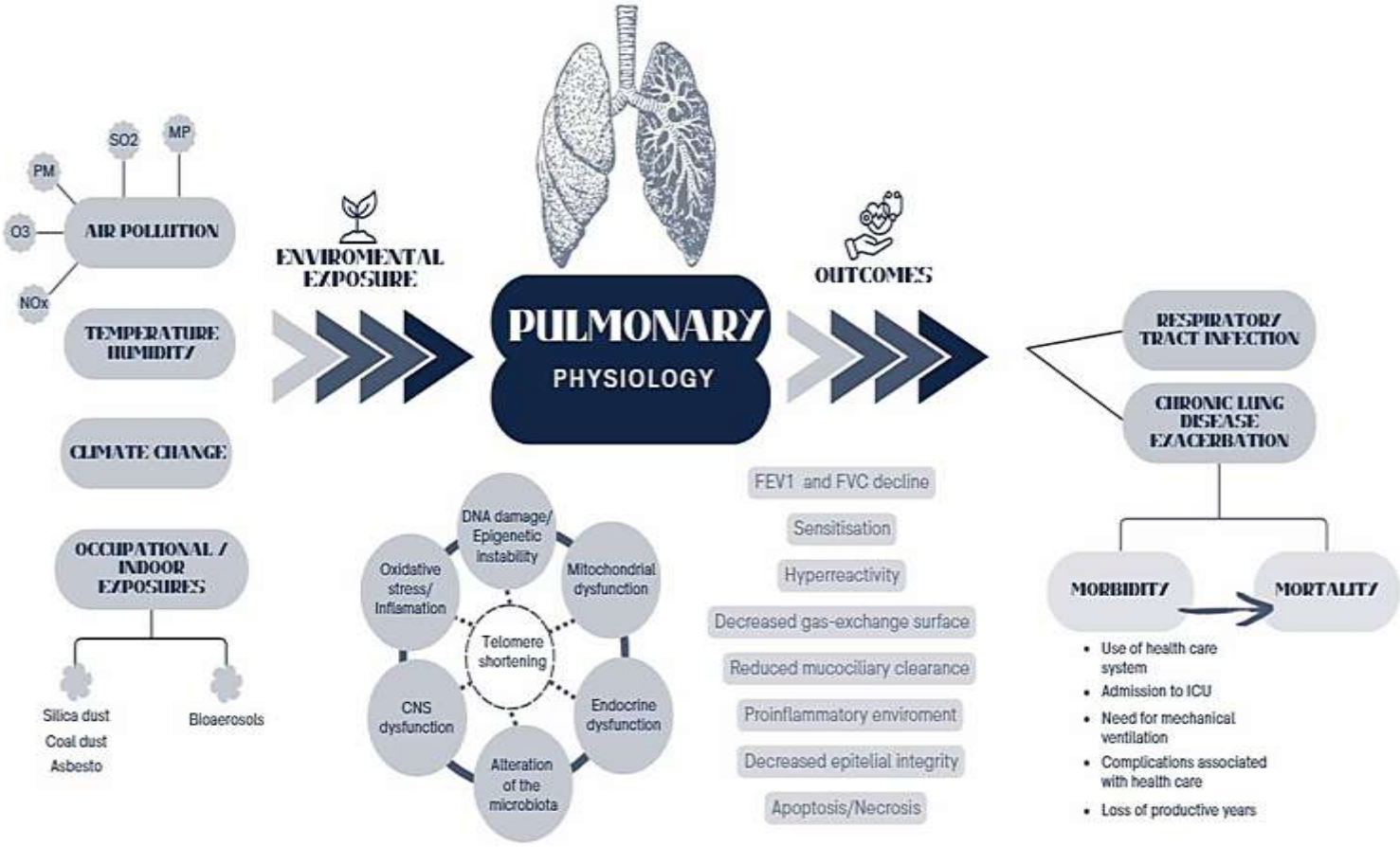

Figure 1: provides a summary of the effects of environmental conditions on lung physiology.

One of the primary characteristics of aging is the compromise of cellular mechanisms, which mirrors the patterns observed during cellular senescence. Telomere dysfunction triggers p53-mediated cellular growth arrest, senescence, and apoptosis, contributing to progressive atrophy and functional decline in tissues with a high turnover.

Telomeres exhibit high sensitivity to reactive oxygen species (ROS), resulting in telomere shortening and dysfunction characterized by decreased Sirtl1 gene expression. The accumulation of damage leads to apoptosis and depletion of progenitor cells, whereas repeated damage to type II epithelial cells culminates in pulmonary fibrosis and cellular senescence.

In the respiratory system, epithelial cells fail to facilitate re-epithelialization following injury, whereas fibroblasts generate a cellular matrix abundant in collagen.

The impact of environmental factors on the respiratory system can be quantified through the assessment of pulmonary function and markers of systemic inflammation, with spirometry being the most commonly employed method. The parameters to be evaluated are contingent on the type of pollutant and its deposition area, which are determined by their physicochemical characteristics.

Exposure to environmental pollutants has generally been linked to a reduction in FEV1 and FVC

Although functional impairment may appear minimal with an annual decrease in FEV_1 of 7-9 mL, it is important to note that these changes are likely influenced by the magnitude and intensity of exposure.

The aforementioned pathophysiological changes are accentuated in susceptible or high-risk populations, considering those with a low antioxidant defense potential.

Within this population, we find that

- Children

  Physiological alterations lead to an increased exposure magnitude.
  - Elevated respiratory frequency and higher level of ventilation per unit body mass.
  - Nasal respiration, characterized by reduced particle filtration efficiency.
  - An underdeveloped innate and adaptive immune system

Exposure to environmental contaminants in children leads to allergic sensitization and increased peripheral airway resistance.

- Elderly/Fragile individuals

  Repeated exposure results in a decline in lung function that is directly proportional to age, which is attributable to diminished lung elasticity and diaphragmatic strength.
  Distal flow obstruction accompanied by heterogeneous ventilation is exacerbated by reduced mucociliary clearance and ineffective coughing mechanisms.

- Athletes

  Physiological adaptations associated with exercise, such as increased tidal volume, elevated respiratory rate, and the transition to oral/nasal breathing, which exposes the airways to unfiltered and unconditioned airflow, contribute to increased exposure to environmental contaminants during athletic training.

- Pregnant women

Environmental pollution is associated with adverse outcomes such as preterm delivery, low birth weight, and impaired lung

Both the pregnant woman and the fetus are subject to environmental contamination. The physiological changes associated with pregnancy increase the risk of in utero exposure by promoting the deposition of particles in the smaller airways due to factors such as increased minute ventilation, elevated resting tidal volume, and reduced anatomical dead space.

Environmental Factors Affecting Pulmonary Function

Air Pollution

Environmental pollution is defined as the presence of undesirable chemical, physical, or biological substances in the atmosphere that adversely affect human health.

Air typically comprises a combination of pollutants and non-pollutant materials originating from natural sources, such as sand, dust, volcanic activity, and forest fires, as well as from anthropogenic activities, including combustion, agriculture, waste incineration, and motor vehicle emissions.

The primary pollutants and the mechanisms through which they influence respiratory function are discussed below. It is crucial to consider that alterations in pulmonary function are directly proportional to the exposure to various pollutants.

- **Particulate Matter (PM)**

  Particulate matter (PM) is a mixture of aerosolized microscopic particles in the solid or liquid state and is generally found in a mixture of pollutants. It is mainly generated by emissions from vehicles and industrial factories and is the environmental pollutant most associated with poor adverse respiratory outcomes.

  The particles are classified based on their aerodynamic diameter into three categories: coarse (2.5 - 10 μm), fine (<2.5 μm), and ultrafine (<0.1 μm).

  Elevated concentrations of PM2.5 and/or PM10 have been linked to the worsening of respiratory symptoms, leading to increased utilization of healthcare services and a rise in public health expenditures.

Short- and long-term exposure to PM has been linked to inflammatory markers such as C-reactive protein (CPR), tumor necrosis factor (TNF-α) and interleukins (IL-6, IL-8).

PM generally influences the respiratory epithelium and immune cells, inducing a pro-inflammatory and pro-oxidant state that ultimately results in damage to adjacent structures. Its effects are primarily characterized by the induction of epithelial barrier dysfunction, with direct damage leading to the production of reactive oxygen species (ROS) and disruption of cellular pathways, including mitochondrial alterations.

Damage to the epithelial protective barrier results in (a) the propagation of an exaggerated inflammatory response and (b) upregulation of airway remodeling cascades.

This pro-inflammatory environment leads to metaplasia and hyperplasia of the mucus-secreting cells. Ciliary function, which is responsible for 80-90% of pathogen clearance, is diminished in individuals exposed to environmental contamination, rendering them susceptible to cycles of inflammation and infection. In the long term, these repeated cycles can result in allergic sensitization (via immunoglobulin E) and irritant effects on the airway.

The erratic remodeling phenomena triggered by environmental pollution are characterized by an imbalance between the action of proteases and the activity of antiproteases, which finally leads to the degradation and development of pulmonary fibrosis.

Finally, the International Agency for Research on Cancer (IARC) classified PM as carcinogenic owing to its association with lung cancer.

PM with a diameter <2.5 μm ($PM_{2.5}$) can enter the tracheobronchial tree and deposit in the smaller airways. These particles may contain transition metal and organic aerosols that cause free oxygen radicals (ROS) and inhibit the activity of antioxidant enzymes in the lung parenchyma, leading to the methylation of CpG sites.

Exposure to $PM_{2.5}$ concentrations exceeding 10 μg/m3 is correlated with a 1.4-2.5% increase in health service consultations

DNA methylation contributes to premature aging by modifying DNA methylation patterns, which leads to the upregulation of proinflammatory cytokines (IL-6, IL-1ß, TNF-α), chemotactic molecules (IL-8 and MCP1), and acute phase reactants.

An increase in $PM_{2.5}$ concentration exceeding 2.4 µg/m3 results in a reduction of 101.7 mL in FEV1

These alterations induce mucus hypersecretion by epithelial cells, leading to airflow obstruction and the infiltration of neutrophils and macrophages, whose proteases compromise the epithelial protective barrier.

Local inflammatory responses induce mitochondrial dysfunction, reduction in epithelial barrier tight junction proteins, diminished viability of epithelial progenitor cells, and telomeric shortening. These senescent changes, coupled with limited regenerative capacity, foster a cycle of impaired healing and an inflammatory milieu characterized by aberrant alveolar remodeling and fibrosis.

- **Ozone (O_3)**

Tropospheric ozone is generated when emissions from industrial facilities and motor vehicles undergo chemical reactions in the presence of ultraviolet light. Ozone molecules possess oxidative properties that enable them to interact readily with lipids, proteins, and various acids.
As these particles are not filtered by the upper airway, they facilitate deposition in the lower respiratory tract and interaction with the epithelial barrier of the respiratory tree, leading to barrier dysfunction.

Environmental concentrations of ozone (O_3) ranging from 0.2 to 0.6 ppm have been correlated with indicators of cellular damage in bronchoalveolar lavage, allergic sensitization in children, and bronchial hyperreactivity.

The interaction of O_3 with epithelial cells modifies the expression and structure of tight junctions, thereby increasing capillary permeability and initiating a local inflammatory response mediated by cytokines and reactive oxygen species (ROS).

Exposure to O_3 reduces mitochondrial energy reserves, diminishes oxygen consumption, and activates the NLRP3 inflammasome, a protein complex that induces inflammation-mediated cell death, ultimately leading to destruction of the alveolar wall.

- **Oxidizing gases: Sulfur Dioxide (SO_2), Nitrogen Oxide (NO)**

Analogous to PM and O_3, the effect of oxidizing gases on the respiratory epithelium is determined by their oxidizing capacity, which induces epithelial barrier dysfunction through the production of reactive oxygen species (ROS) and inflammatory markers. This sequence of events is ultimately associated with the pathophysiology of chronic lung diseases.

As a by-product of fossil fuel combustion, SO_2 is a toxic gas that significantly contributes to environmental pollution in industrialized nations. Owing to its high solubility, the effects of SO_2 are primarily confined to the upper airway. The inhalation of SO_2 results in its metabolism to sulfuric acid, which subsequently enhances bronchial hyperreactivity and bronchoconstriction.

Sulfur dioxide (SO_2) leads to a reduction in peak expiratory flow (PEF) at concentrations exceeding 1 ppm.

Furthermore, it reduces mucociliary clearance, thereby increasing mucus viscosity and facilitating colonization of pathogens within the bronchial tree. Ultimately, this process promotes the infiltration of inflammatory cells and local tissue remodeling.

Nitrogen Oxide (NO) is a water-soluble gas that is produced during combustion. Owing to its low solubility, it is deposited in lower airways. Its metabolism leads to its conversion into acids, specifically nitrous acid (HNO_2) and nitric acid (HNO_3). These substances compromise the epithelial cell barrier, resulting in chemical pneumonitis and pulmonary edema.

Damage to the epithelium initiates an immune response characterized by the release of inflammatory cytokines, including IL-4, IL-5, and IL-13, and an increase in eosinophil-mediated inflammation. Furthermore, it reduced the production of anti-inflammatory cytokines by alveolar macrophages, thereby suppressing the immune response.

In children, exposure to NO_x has been linked to alterations in lung function, specifically manifesting as obstructive flow patterns.

Dysregulation of the immune system, in conjunction with increased vascular permeability and airway hyperreactivity, increases the susceptibility to respiratory infections.

Air pollution is correlated with an increased severity of chronic obstructive pulmonary disease (COPD) and asthma exacerbations, as evidenced by higher hospital admissions during periods of poor air quality, which deteriorates overall function. Pollutants increase the risk of respiratory mortality and hospital admissions, particularly when combined with elevated temperatures. The interaction between air pollution and temperature can exacerbate lung dysfunction, especially in vulnerable populations such as the elderly.

- **Microplastic fibers**

In recent years, the presence of microplastics as a component of environmental pollution has garnered significant attention.

These minute plastic particles, measuring less than 5 mm in length but greater than 0.1 μm, are prevalent in cosmetics, textiles, single-use plastics, and vehicle tires. Owing to their morphology, they exhibit extensive dispersion, not only in air but also in water, making contact with them unavoidable. Their diminutive size facilitates their penetration into tissues.

The inhalation of these compounds and their subsequent deposition on the epithelial barrier initiates an inflammatory response, increases interstitial fluid, and bypasses reabsorption mechanisms, ultimately leading to apoptosis of barrier cells and deterioration of lung function. Recent studies have even begun to suggest their classification as a deposition disease akin to occupational exposure.

Temperature and Humidity

Changes in meteorological conditions can amplify the impact of climate change by influencing the formation, transport, and dispersion. Extreme temperatures, whether high or low, affect the functioning of the respiratory system, a phenomenon observed not only in individuals with chronic lung disease, but also in previously healthy populations.

Exposure to excessive heat enhances the formation of ground-level O_3, worsening the lung induced changes. In addition, it increases the risk of bronchospasm due to airway irritation as well as the effects of dehydration and increased viscosity of bronchial secretions, which ultimately reduces oxygen uptake. Heat can disrupt the airway epithelial barrier, leading to increased airway inflammation and hyper-reactivity, which may exacerbate conditions such as asthma and allergic rhinitis. Extreme heat is associated with increased morbidity and mortality in patients.

Warm temperatures have an inverse impact on the Peak Expiratory Flow (PEF)

Extreme warm temperatures are a risk factor for COPD exacerbation in female patients and in male and female patients aged > 65 years.

For each 1°C reduction in temperature, the likelihood of seeking consultation for the exacerbation of chronic respiratory

Low temperatures lead to drying and cooling of the airways, leading to an increase in airway resistance, accompanied by excessive mucus production and an enhanced local inflammatory response. These pathological reactions exacerbate the obstructive patterns characteristic of pulmonary diseases, thereby intensifying chronic symptoms and increasing the demand for rescue therapies and healthcare consultation. Conversely, extreme cold is associated with increased morbidity and mortality in chronic obstructive pulmonary disease (COPD), with a significant impact observed in European populations.

RH plays a crucial role in maintaining healthy environments and is essential for regulating moisture levels and preventing the growth of harmful microorganisms. Variations in relative humidity (RH), whether increasing or decreasing, are linked to the decline in pulmonary function, particularly in the deterioration of peak expiratory flow (PEF). It has been proposed that lower RH may elevate the risk of viral transmission and augment airborne concentrations by reducing their dispersion.

When humidity is coupled with elevated temperatures, it can further aggravate pollutant-related lung dysfunction, underscoring the intricate interaction between meteorological factors and air pollution. Humidex, an index of thermal discomfort, has been demonstrated to correlate with an increase in hospital admissions for obstructive lung disease during the summer months.

Extreme temperatures increase COPD mortality:

- *Heat RR 1.16 (95%CI 1.08-1.26; P<0.05)*
- *Cold RR 1.32 (95%CI 1.20-1.46; P<0.05)*

It is crucial to emphasize that in published population studies, the relationship between changes in pulmonary function and temperature or relative humidity conditions exhibits a linear pattern. Nevertheless, this relationship appears to be synergistically influenced by environmental pollutants. These factors are mainly associated with epidemic outbreaks.

Climate change

The relationship between climate change and air composition is direct, with both factors exerting an amplifying effect on respiratory function. Global warming is primarily caused by greenhouse gas emissions such as carbon dioxide (CO_2), methane (CH_4), and nitrous oxide (N_2O), mainly from fossil fuel combustion, deforestation, and agriculture.

During extreme weather events, photochemical reactions between precursor emissions increase during heatwaves, producing ground-level O_3 that irritates the respiratory system. Storms and transportation infrastructure contribute to dust and particle emissions, whereas wildfires release vast quantities of PM and other pollutants, which can travel long distances. Wildfires induced by climate change emit PM and black carbon, deteriorate air quality, and accelerate ice melting, thereby hastening climate change.

These interactions create feedback loops that amplify the air quality and respiratory health effects. Understanding their complex interplay is critical for mitigating the adverse effects of climate change and air pollution on human health and environment.

Occupational Exposures

- **Silica Dust**

The inhaled silica particles are deposited and crystallize within the airways. Upon phagocytosis by resident macrophages, reactive oxygen species (ROS) and pro-inflammatory cytokines are released. Animal models have demonstrated that these inflammatory changes interact with telomeric protein complexes, resulting in DNA damage to type II epithelial cells. The loss of alveolar cells initiates aberrant healing mechanisms, characterized by abnormal fibroblast proliferation and increased collagen production surrounding inhaled particles. Consequently, interstitial fibrosis occurs, which leads to decreased lung compliance and impaired gas exchange.

- **Coal Dust**

Coal particles are not subject to elimination and consequently undergo phagocytosis by macrophages within the alveolar space. This process induces the release of TNF-α and IL-6, which in turn stimulate the infiltration of inflammatory cells that compromise the integrity of the alveolar walls. The recruitment of fibroblasts, facilitated by IGF-1 and PDGF, promotes local proliferation, leading to upregulation of collagen production and the formation of characteristic pneumoconiosis lesions. These lesions manifest as areas of localized emphysema accompanied by nodules that distort the architectural structure and adversely affect function.

- **Asbestos**

Asbestos fibers are highly durable minerals that have historically been utilized in construction because of their strength.

Buildings constructed with these materials can release asbestos particles when deteriorated. Upon inhalation, these particles are deposited in the airways, and because of their size, they cannot be phagocytosed by alveolar macrophages. This incomplete phagocytosis results in biomineralization and formation of metal-rich envelopes.

Animal models have demonstrated the production of reactive oxygen species (ROS) in alveolar epithelial cells, mesothelial cells, and macrophages. Persistent oxidative stress leads to DNA damage, activation of apoptosis in type II alveolar epithelial cells, expression of p53 in progenitor cells, and failure to activate repair mechanisms. Abnormal fibroblast proliferation results in interstitial fibrosis.

Agent	Found in…	At risk population	Results in
Silica dust	Granite and sandstone rocks	Any activity that requires breaking ground or handling stone	Silicosis
Coal dust	Coal mines, power plants, storages, Industrial Facilities	Mining, transporters and processing workers	Neumoconiosis
Asbestos	Pre-1980s buildings, industrial sites (power plants, factories, refineries, railroads), Automobile parts (Brakes, clutches, gaskets), soils and rocks	Construction workers, shipyard workers, firefighters. Family members of exposed workers. Residents near asbestos mines or factories, people living in older homes.	Asbestosis

Indoor Exposures (Bioaerosols)

Poorly ventilated environments may harbor biological contaminants including bacteria, viruses, and fungi. The inhalation of extracellular vesicles and their subsequent accumulation in the lower respiratory tract can activate the innate immune response, trigger the production of inflammatory cytokines, and lead to structural destruction of alveolar septal components. Repeated exposure ultimately results in distortion of alveolar walls, thickening due to collagen deposition, glandular hyperplasia, and emphysema.

Public Health Implications and Preventive Strategies

The formulation and execution of effective strategies for the primary and secondary prevention of lung diseases resulting from exposure to environmental factors have been integrated into global public health policies. The adaptation of these strategies is contingent on the geographical region, public policies, and socioeconomic conditions of the environment in which they are implemented.

In general, the proposals include

- Portable or centralized air filters to decrease pollutant concentrations, such as HEPA filters (high-efficiency particulate air) in filtration system ducts, which reduce particulate matter concentrations in indoor environments
- Air pollution monitoring networks
- Promotion of the development and utilization of clean energy sources
- Avoidance of strenuous physical activity in open spaces during pollution peaks
- Smoking cessation
- Reduction of occupational exposure: Extraction systems, individual prevention (personal protective equipment, removal of particles from skin and clothing), secondary prevention (early detection)
- Completion of vaccination schedules, particularly in populations with chronic pulmonary conditions (>65 years)
- Inclusion of access to green spaces in territorial development plans
- Protective measures for lung cancer patients during periods of high air pollution necessitate systematic measurement

To date, no pharmacological regimen has demonstrated long-term efficacy in preventing or mitigating environmental exposures. Previous studies on NSAIDs, Vit B, Vit C, Vit E. Ultimately, all of these measures must be accompanied by adequate access to healthcare systems.

Conclusion

The relationship between environmental conditions and respiratory health is complex and multi-faceted. Its impact on the respiratory system is extensive, as it generates oxidative stress and creates a local proinflammatory environment, leading to epithelial damage and distortion of the lung parenchyma owing to ineffective repair mechanisms. The extensive medical literature underscores the need for ongoing research and public health interventions to mitigate these effects.

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