Respiratory Medicine
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Emily J. Pennington *Editors*

Lung Health and the Exposome

How Environmental Factors Influence Lung Health

ATS American Thoracic Society
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Respiratory Medicine

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How Environmental Factors Influence Lung Health

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We help the world breathe®
PULMONARY • CRITICAL CARE • SLEEP

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Preface

The exposome encompasses all exposures through a person's life – including environmental and occupational exposures – and how those exposures impact health. The increased emphasis on climate change and its environmental impact has also led to an increased interest in all of the ways our environment impacts our own health. As we exchange air, our lungs are constantly exposed to the surrounding environment, amplifying the role that the exposome plays in lung disease. We wanted to use this book to explore all of the ways our exposome affects lung health.

Tobacco-related effects on lung health is probably the first exposure that comes to most clinicians' mind when considering exposome effects on respiratory disease. However, there are a number of other exposures that also impact multiple different lung diseases. Air pollution greatly influences airways disease and is an important but under-recognized contributor to poor disease control and exacerbations. Occupational lung disease is a broad category of multiple exposures that can lead to airways disease, hypersensitivity pneumonitis, and interstitial lung disease. While clinicians may be broadly familiar with these exposures and their effects, we hope these chapters help to improve your understanding of how to evaluate for these exposures, mitigate their effects, and treat lung diseases that develop from them.

A number of other pulmonary conditions have well-known environmental triggers; however, there are gaps in knowledge regarding their true impact. For instance, approximately 10–20% of lung cancers occur in patients who never smoked, and we have only begun to understand the impact of radon, occupational carcinogens, and other exposome exposures on this disease. Pulmonary hypertension is another area in which the impact of exposome has not been fully explored . The intent of this book is to also introduce new ideas and generate interest for future research which may expand our understanding of the influence of the exposome on lung health.

Finally, we wanted to include two areas of timely interest and concern which need significant attention for the future of lung health: recreational inhalants and climate change. The recent spike in e-cigarette and vaping-related lung injury has prioritized the need to evaluate and manage the impact on new forms of smoking tobacco and recreational drugs on lung health. We are also behind in our dissemination of knowledge and understanding of the full impact of climate change on our

health, both from catastrophic incidents as well as slower, longer-term changes to our environment.

We are both extremely grateful to our authors who generously gave their time, effort, and expertise to advance knowledge in this area. We hope this textbook will provide a comprehensive overview of the impact the exposome has on our lung health and allow clinicians to better incorporate these ideas into their clinical practice and advocacy around these conditions.

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Air Matters: The Effect of Ozone and Traffic Related Air Pollution on the Airways

Neha Solanki

Introduction

Traffic related air pollution (TRAP) is considered a culprit for the exacerbation of various airway diseases such as chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis. TRAP is a mixture of (1) particulate matter (PM) derived from combustion (including elemental or black carbon), (2) non-combustion sources (e.g.- road dust, tire wear, brake wear), and (3) primary gaseous emissions including nitrogen oxides along with secondary pollutants such as ozone. Together, these sources contribute to a decline in pulmonary health. As there are several contributors to TRAP, it is important to learn how they all contribute individually and also in aggregate. In this article, we will explore the role of nitrogen oxides, ozone and particular matter in the development and control of lung diseases such as asthma, COPD, cystic fibrosis and non-cystic fibrosis bronchiectasis. Epidemiologic and pathophysiologic data will be presented, and the role of air quality regulations and public policy will be discussed. Furthermore, we will touch upon the advanced role of a clinician not only to offer individualized education but to also be engaged in advocacy beyond the bedside.

Particulate Matter, Nitrogen Oxides, and Ozone

TRAP consists of particulate matter and nitrogen oxides among other gases. Ozone can also present with TRAP because fossil fuels such as gasoline emit gases like nitrogen dioxide which undergo environmental reactions to form ozone. Particulate

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matter (PM) is one component of TRAP, characterized by its size. In addition to automobile combustion, particulate matter comprises of black carbon, metals, dust particles, soil particles, and organic chemicals as well as other particles such as sea salt [1]. A mixture of solid and liquid particles in our environment, particulate matter can be further divided into three categories: coarse particulate matter ranging between 2.5 and 10 micrometers in size ($PM_{2.5–10}$) which primarily deposit in the primary bronchi; fine PM ranging from 0.1 to 2.5 micrometers in size (0.1–2.5 μm) which penetrate the alveoli and terminal bronchioles; and ultrafine PM which are particles less than 0.1 micrometers in size (0.1 μm) which can cross cell membranes and interact with cellular structures [2] (Fig. 1). These different sizes of particulate matter have different clinical and pathological effects on the human lung because the smaller the particles are, the more they are able to infiltrate the lungs. The different health effects that are observed for particulate matter are due to the weight and the aerodynamics of the particle in the human lung [3]. More than 50% of the total PM emissions are related to road traffic [4], and in the United States, 11–19% of people live within a few hundred meters of major roads and so are exposed to particulate matter of varying sizes and with varying effects on the lung [4]. Individuals living in residential areas that are in close proximity to major roadways have been shown to have an increase in adverse health effects thought to be associated with air pollution [5].

Due to their size and ability to travel to the bronchi, $PM_{2.5}$ emissions are clinically significant and are composed of tailpipe exhaust, brake wear, tire wear, and

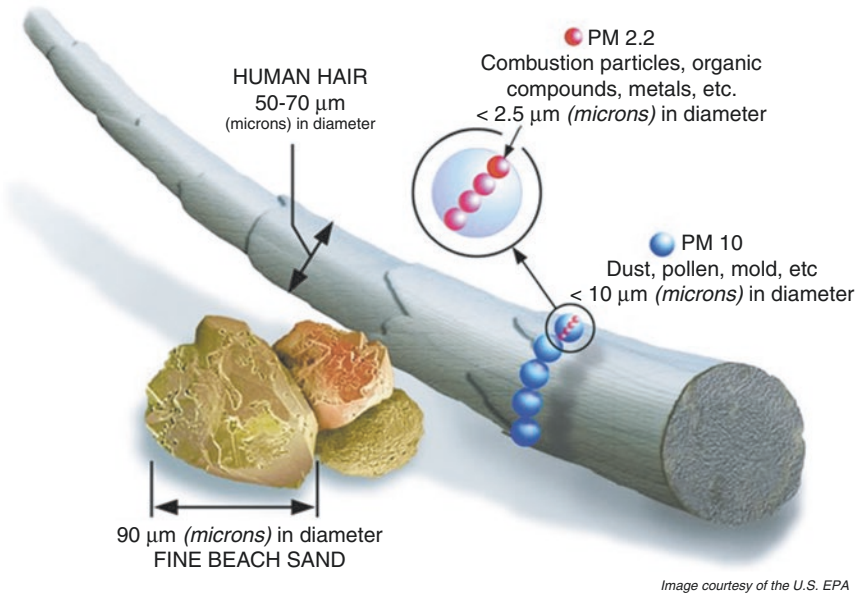

Fig. 1 This image demonstrates the size of different types of particulate matter and how they compare with a strand of hair [6]. (U.S. EPA-Public Domain)

resuspended dust [5]. Other major chemical contributors to $PM_{2.5}$ mass are sulfate, nitrate, ammonium, and organic carbon [7]. While the best known particles that comprise $PM_{2.5}$ include biomass burning, gasoline combustion, diesel combustion, dust, and industry, bioaerosols are also included within this category of particulate matter. Bioaerosols are found in agricultural communities and consist of agriculture dust, pollen, diesel fuels from tractors, and aerosolized endotoxin from livestock [8]. Rural and urban sites alike are affected by particulate matter in the air; though urban areas have a higher burden of TRAP, the effects of air pollution cannot be completely discounted in more rural areas.

Meanwhile, nitrogen dioxide (NO_2), derived from the oxidation of nitric oxide, is a toxic respiratory gas considered to also be a part of TRAP [9]. There are seven oxides of nitrogen that are found in the environment; however, nitric oxide (NO) and nitrogen dioxide (NO_2) are the two principal nitrogen oxides (also known as NOx) associated with combustion sources [10]. Nitric oxide is oxidized rapidly in air to form nitrogen dioxide by available oxidants such as ozone in ambient air, meanwhile, oxides of nitrogen are formed by combinations with oxygen and nitrogen at high temperatures during the combustion process [10].

The predominant primary sources of nitric oxides are motor vehicle exhaust, cigarette smoke, power plants, and off-road equipment. Another example of nitrogen oxide exposure occurs in the setting of silo filler's disease [11]. This etiology of the toxic nitrogen oxide gases and their derivatives arise as a result of the occupational hazard associated with the storage of crops in farm silos causing toxic levels of NO, NO_2, and N_2O (nitrogen oxide, nitrogen dioxide and dinitrogen oxide, respectively) to be produced when these silos are filled with corn and grain [11]. Indoor sources of nitrogen oxides include tobacco smoke and gas, wood, oil, kerosene, and coal burning appliances, such as stoves [10]. Inhalation is the major route of exposure [10].

In addition to particulate matter and nitrogen oxides, ozone is another component of urban smog. TRAP and ozone can coexist in the presence of volatile organic compounds (VOCs) that react with heat and sunlight to produce ozone. However, ozone is a seasonal pollutant as it is made in the presence of heat and sunlight, while PM pollution is present throughout all seasons. Ozone exposures have been shown to trigger asthma exacerbations and have been associated with reductions in the rate of lung development [12]. Airway changes occur when ozone exposure triggers oxidative stress and damage, airway remodeling, inflammatory pathways and enhancement of respiratory sensitization to aeroallergens [12]. According to the Health Effects Institute (HEI) 2019, when ozone is in the stratosphere, it plays a protective role by shielding the Earth from harmful ultraviolet radiation [13]. However, when ozone is near ground level known as the troposphere, it acts a greenhouse gas and an air pollutant with harmful effects on human health [13]. Per HEI 2019, ground level ozone is produced by transportation vehicles that emit chemical precursors such as nitrogen oxides into the atmosphere which react in the presence of sunlight to form ozone [13]. Therefore, ozone it is a secondary pollutant because it depends on sunlight and fossil fuels [12].

In summary, TRAP is composed of many individual toxic gases and particulate matter that all contribute to the overall airway diseases and respiratory health. Detailed descriptions of these associations will be presented further in the next section.

Air Pollution (TRAP and Ozone) Effects on Lung Disease

TRAP and COPD COPD, the third leading cause of mortality worldwide, is a chronic inflammatory respiratory disease characterized by an enhanced inflammatory response in the airways and lungs to noxious particles or gases. Long and short-term air pollution can increase mortality in COPD patients. In fact, the impact of air pollution is higher on the mortality of COPD patients than it is in the general population [14].

Recently, the UK biobank, a national cohort study of half a million participants aged 40–69 years of age in urban areas, was used to examine whether air pollution was associated with lung function and COPD [15]. Ambient concentrations of particulate matter and nitrogen oxides in air pollution were found to be associated with lower lung function and increased COPD prevalence [15]. Exposure to 5 μg/m^3 of $PM_{2.5}$ led to a lower FEV_1 and lower FVC (forced expiratory volume in 1 second, forced vital capacity, respectively) [15]. Additionally, long term exposure to ambient $PM_{2.5}$ was associated with an increase in the incidence of COPD. COPD incidence, prevalence and morbidity are all affected by TRAP which comprises of $PM_{2.5}$. Notably, mere compliance with WHO air pollution levels for $PM_{2.5}$ could prevent 11% of all incident asthma cases, while more stringent air pollution levels could prevent up to 33% of incident cases [16]. Evidence to date suggests that exposure to high levels of PM, either acutely or chronically, is associated with increased hospitalization rate, incidence of COPD and loss of lung function [17].

Ozone and COPD While particulate matter is toxic to patients with COPD, ozone is harmful as well. One cohort study investigated the development of emphysema on sequential chest CTs upon exposure to ozone from 2000 to 2018 in six metropolitan regions throughout America [18]. Amongst ozone, particulate matter, and nitrogen dioxide, ozone had the most robust association with severity of COPD. Baseline ambient ozone was significantly associated with a fast decline of the forced expiratory volume in 1 second. Another multicenter cross-center study investigated the effects of ambient ozone on participants over a 10 year range with data from the Air Pollution Study which is part of SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) [19]. In addition to Chest CTs, the participants also had 6 min walk tests, modified Medical Research Council (mMRC) Dyspnea Scale, COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), post bronchodilator forced expiratory volume in the first second of expiration (FEV_1) % predicted, and self-report of exacerbations. Long-term historical ozone exposure was found to be associated with reduced lung function, greater emphysema and air trapping on CT scans, worse patient-reported outcomes, and

increased respiratory exacerbations for individuals with a history of heavy smoking [19]. Patients with emphysema exposed to higher ozone levels experience increased hospitalizations and mortality even if patients have normal pulmonary function testing, demonstrating that those individuals with relatively preserved lung function still experience adverse effects with ozone exposures [18].

Though the relationship between NO_2 and its effect on COPD is still being investigated, it is known that NO_2 from long-term traffic exposure has been found to cause harm in patients with COPD [20]. The overall relative risk of COPD increased by 2.0% when exposed to 10 μg/m^3 of NO_2 exposure [20]. With a 17% increase of 10 μg/m^3 of NO_2, a 1.3% increase in hospital admissions was noted for COPD as well as an 2.6% increase in mortality [20].

TRAP in Asthma TRAP is associated with increased incidence of asthma throughout childhood, and the magnitude of the risk increases with age [21]. The Cincinnati Childhood Allergy and Air Pollution Study is a prospective birth cohort study that has shown that early childhood exposure to TRAP is associated with wheezing at age 1 and 3 years [22]. A follow up longitudinal study found that the same children exposed to high levels of TRAP at the time of birth were nearly twice as likely to experience persistent wheezing at 7 years of age [22]. The Southern California Children's Health study also demonstrated that TRAP exposures later in childhood are associated with impaired lung growth and increased incidence of asthma. No significant associations between air pollution exposure and childhood asthma prevalence were found among five European birth cohorts [23]. These differences may be due to the fact that the children in the European birth cohorts have different early life exposures than children in the American birth cohorts [23].

Ozone in Asthma Real-world exposures to ozone have an effect on asthma. Asthma severity is graded by emergency department visits, hospital admissions for asthma, as well as respiratory symptoms, and lung function changes in patients with asthma [24]. Short-term exposures to air pollution can increase airflow obstruction in children with and without asthma [25]. An increase in ozone, CO, and NO_2 exposure has specifically been associated with reductions in lung function levels for both FEV_1 and FVC [26].Longer exposure to ozone was associated with worsening airflow obstruction as measured by FEV_1/FVC [26]. This airway obstruction reflects airway wall remodeling related to repeated exposures to ozone and other pollutants [26]. Patients with asthma can experience as much as a 20% decrease in FEV_1 at 0.25 parts per million (ppm) of ambient ozone levels [27]. Furthermore, 1 h of exposure to 0.12 ppm ozone can cause early bronchoconstriction in specifically sensitized asthmatic subjects [28]. Lung function response to ozone shows large variation between individuals. When patients with mild atopic asthma (sensitive to dust mites) are exposed to clean air and then to 0.16 ppm of ozone for several hours over at least 4 weeks, pulmonary function studies measured before and after exposures demonstrate a mean 9.1 ± 2.5% decrement in FEV_1 observed because of what appears to be a priming effect of ozone ($p < 0.01$) [29]. Ozone also may increase an individual's reactivity to allergen after ozone exposure and potentiate the effect of an existing allergen after ozone exposure [29]. The outcomes of short-term expo-

sure to ozone relate to asthma severity [24]. Long term ozone exposure may also contribute to asthma development, and in adult-onset asthma, men, but not women, appear to be at increased risk [30].

TRAP in Bronchiectasis Bronchiectasis is different from asthma and COPD in terms of its etiology and its pathology. The etiology of bronchiectasis may vary. For the purposes of this chapter, they will be divided into CF bronchiectasis and non-CF bronchiectasis. Non-cystic fibrosis (non-CF) bronchiectasis is a chronic respiratory condition in which patients have dilated bronchi which impair host defense and lead to chronic colonization with bacteria and airway inflammation [31]. Clinically, this is characterized by recurrent respiratory infections, cough and sputum production [31]. Cystic fibrosis (CF) bronchiectasis is a hereditary disorder causing exocrine glands to produce thick mucus which blocks bronchi, resulting in respiratory infection.

Viruses are commonly thought to be the culprit to trigger acute exacerbations of bronchiectasis. However, it is possible that air pollution and specifically TRAP could also be responsible for acute bronchiectasis exacerbations. Exacerbations are known to increase risk of mortality, hospital admissions, lung function decline and ultimately death [32]. The effects of air pollution on bronchiectasis have not been studied as much as the effect of air pollution on asthma. However, the existing studies do demonstrate that the annual exposure to TRAP is associated with an increased risk of bronchiectasis exacerbations and a decrease in lung function [33]. Thus, there is a positive correlation between TRAP and CF exacerbations.

Non-CF bronchiectasis has been studied less than CF bronchiectasis. Non-CF bronchiectasis is influenced by gender, age, smoking history and infection with Pseudomonas aeruginosa. An observational study in Belgium of patients with non-CF bronchiectasis found an association between living near a major road and mortality from TRAP exposure [34]. A case-crossover analysis showed that the risk of having a non-CF bronchiectasis exacerbation increases significantly on days with increased air pollution. For each 10 $\mu g/m^3$ increase in PM_{10} or NO_2, the risk of having a same day exacerbation increased significantly by 4.5% and 3.2%, respectively [33].

COPD, bronchiectasis, and asthma are affected by the particulate matter, ozone, nitrogen oxide derivatives in TRAP, and thus have far ranging health consequences on the lung. Thus, future research must continue to examine acute effects and chronic effects of air pollution on lung health, specifically asthma and COPD and bronchiectasis.

Epidemiology of Traffic Related and Ozone Air Pollution and Lung Health

Traffic related air pollution is a major contributor to outdoor air pollution, especially in developed countries [4]. Outdoor air pollution varies in composition depending on sources, geography, topography, wind direction and speed, ultraviolet radiation and humidity [4].

PM Epidemiology Studies According to the Global Burden of Disease 2019, high levels of particulate matter have been found to have a significant increase in mortality, marking it as the seventh leading cause of mortality throughout the world [35]. The most recent Global Burden of Disease (GBD) highlighted that outdoor air pollution has led to 4.4 million premature deaths globally, a figure which likely underestimates the actual harm [35]. A prospective cohort study of over 8000 individuals in six US cities, mortality was found to be most strongly associated environmental fine particulate matter [36]. Over 300 million children breathe highly toxic air at levels six or more times exceeding international guidelines [37]. Indoor and outdoor air pollution is linked to 1 in 10 deaths in children under 5 years of age. Of these children, 20% of these deaths are attributed to outdoor air pollution [38].

Nitrogen Dioxide Epidemiology Studies Systematic reviews and meta-analyses have assessed evidence from cohort studies from 2013 to 2014 and have found associations between NO_2 concentrations and mortality from respiratory diseases. According to the US Environmental Protection Agency Integrated Science Assessment, the toxicological and epidemiologic evidence across a wide range of health end points concluded that the evidence is suggestive of but not sufficient enough to infer a causal relationship between the long-term exposure to NO_2 and mortality among adults [39]. A 2016 meta-analysis found positive associations between NO_2 and all cause respiratory mortality with significant evidence of substantial heterogeneity between studies [9].

In a study that measured nitrogen dioxide at 67 sites in Montreal, Quebec, Canada investigators found TRAP was highly concentrated near roadways but declined rapidly within 150–300 m of the major road [40]. It has therefore been extrapolated that people who live near roadways are at higher risk of developing airway disease. However, the association between nitrogen oxides and adult-onset lung disease, specifically COPD, asthma, and non-CF bronchiectasis, still requires more research. Much of the epidemiological relationship between asthma and nitrogen oxides is still under investigation.

Ozone Epidemiology Studies Globally, 9–23 million asthma emergency room visits at all ages in 2015 were attributable to ozone, and ozone represented 8–20% of the 116 million global asthma emergency room visits in total [41]. When compared to twenty-five other countries spanning North America, Europe, Asia, and Latin America in 2015, India and China had the most estimated asthma emergency room visits (ERV) attributable to air pollution, respectively, contributing 23% and 10% of global asthma ERVs [41]. This is thought to be attributable to the high population density, heavy traffic and resultant poor air quality.

An earlier study done by Friedman and colleagues studied the impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma [42]. They found that reduced traffic congestion due to changes in traffic patterns and use of public transportation diminished atmospheric ozone levels in the city. This temporal reduction in air pollution was associated with fewer acute asthma visits among children [42].

In a meta-analysis regarding ambient ozone with regard to mortality, hospital admissions, and emergency room visits in adults, a 10 parts per billion (ppb) increase in 8 h ozone concentration was associated with a 0.60% (95% CI: 0.40, 0.80) increase in total mortality for younger persons with asthma and a 1.27% (95% CI: 0.76, 1.78) increase for older persons [25]. The authors found that the ozone-mortality relative risk was 0.39% (95% CI: 0.22, 1.00) higher for women than for men [25]. Ozone mortality risk was also 0.66% (95% C: 0.12, 1.12) higher for older populations than younger populations [25]. A subsequent meta - analysis covering the years from 2000 to 2016 found significant associations of NO_2 as well as other pollutants with asthma exacerbations: NO_2 (OR: 1.024; 95% CI: 1.005, 1.043), $PM_{2.5}$ (OR: 1.028; 95% CI: 1.009, 1.047), and ozone (OR: 1.024; 95% CI: 1.005, 1.043) [43]. Only PM_{10} and sulfur dioxide did not demonstrate a significant association with moderate or severe exacerbations of asthma.

Future Epidemiologic Evaluation of Traffic Related and (Ozone) Air Pollution and Lung Health While many epidemiologic studies have helped determine air pollution associations with detrimental aspects to lung health, more sophisticated epidemiology research accounting for multiple variables and confounders are needed. Pollution exposure estimates based upon home address may inaccurately estimate TRAP exposure as they do not consider environmental exposures away from home such as time spent commuting to school or work. Most studies have also examined TRAP exposure windows during the birth year and early-life; however, exposures in later life and exposures of varying durations are inadequately studied [44]. Another gap in the literature is the study of the relationship between air pollution and the onset of asthma in adults [12]. Most studies at this point have looked at the pediatric population as they do not have as many comorbidities as adults often do. TRAP affects people with chronic lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) and non-CF bronchiectasis throughout their lives, and so it is important to refine the ways in which it can be studied [45].

Pathophysiology of TRAP: Particulate Matter, Nitrogen Oxides, Ozone

The understanding of the pathophysiologic mechanisms of ozone and TRAP and lung disease has evolved over time. According to Britain's Committee on the Medical Effects of Air Pollutants, there are four likely mechanisms by which air pollution affects asthma: oxidative stress and damage, inflammatory pathways, airway remodeling, and enhancement of respiratory sensitization of allergens [46]. Oxidative stress and damage are thought to be the most significant contributor to the development, progression, and exacerbation of airway disease. TRAP exposures induce oxidative stress which activates downstream inflammatory pathways. These pathways are known to increase cytokine expression, activate immune cells, and ultimately lead to inflammation in patients with airway disease which can cause airway remodeling and enhance respiratory sensitivity to allergens.

Pathophysiology of Particulate Matter When air is inhaled, large and coarse particles are filtered out and deposited in the nose and the nasopharynx, while smaller particles reach the lower respiratory tract. The particulate matter in air passes down the tracheobronchial tree and particle retention decreases with every new generation of respiratory bronchiole [8]. The smallest particles deposit on the mucosal lining and continue to the alveoli. Toxic particulate matter enter by way of the alveoli and then infiltrate the circulatory system while shepherding airborne toxic substances on their surface area [2]. These toxins can then instigate the inflammatory cascade yielding to airway disease.

Cell culture experiments have shown that particulate matter such as diesel exhaust particles (DEPs) stimulate the innate immune response via the protective layer of specialized airway epithelial cells [47]. Dendritic cells which are located near the airway epithelial cells select and sequester particulates and pathogens [47]. These are the most potent antigen presenting cells (APCs) in the immune system and enhance Th2 lymphocyte response [47]. These dendritic cells then migrate to the mediastinal lymph nodes and stimulate antigen-specific CD4 T cells to secrete proinflammatory cytokines leading to a predominantly neutrophilic IL-17–mediated lung inflammation [47] (Fig. 2). Allergen-sensitized mice exposed to ambient

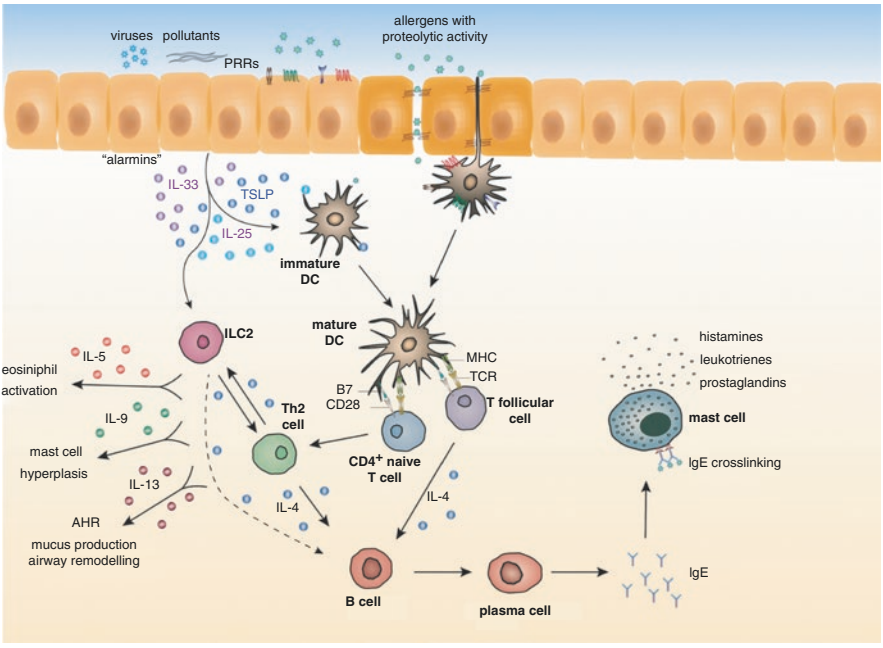

Fig. 2 This image demonstrates pollutants enter the epithelium of the alveoli and stimulate immature dendritic cells to become mature dendritic cells. These dendritic cells go onto to active Th2 cell and increase IL-5, IL-9, and IL-13 which yields eosinophil activation, mast cell hyperplasia, and mucus production and airway remodeling. (With permission from Morianos and Semitekolou [48]. License: https://creativecommons.org/licenses/by/4.0/legalcode)

PM have exacerbated allergic airway inflammation characterized by both IL-17 and type 2 cytokines (IL-4, IL-5, IL-9, IL-13) allowing for a mixed eosinophilic and neutrophilic lung inflammation [47].

In CF and non- CF bronchiectasis patients, particulate matter enhances mitochondrial signaled CF bronchial epithelial cell apoptosis at lower levels of exposure when compared to a healthy controls [49]. In turn, this may impair pathogen clearance [50]. In bronchiectasis, clearance of the pathogen is important, therefore, these patients are more sensitive to particulate matter and the subsequent infections due to impaired pathogen clearance. In asthma, COPD, and bronchiectasis, particulate matter causes inflammation which encompasses delayed neutrophil apoptosis, impaired macrophage phagocytosis, activation of the inflammasome pathways and alterations in the airway microbiome [51].

Pathophysiology of Gaseous Pollutants: Ozone and Nitrogen Oxide Derivatives Ozone plays an important role in the onset and severity of airway disease. The mechanism of structural changes seen in lung diseases such as COPD and asthma have been studied via ozone-induced lung inflammation mouse models [52]. Ozone exposures induce airway inflammation in mice which cause an increased presence of neutrophils and macrophages, high levels of cytokines and chemokines, and emphysematous changes in the lung. In mice, ozone-related inflammatory changes, oxidative stress, airway remodeling, and alveolar destruction result in a persistent inflammatory environment in the lung [53]. Ozone induces a state of inflammation in the mouse model and eventually leads to airway remodeling and a persistent inflammatory environment in the lung, much like the lung of an individual with asthma [52].

Mechanistically, inhaled ozone does not enter cells but reacts with components of the airway lining fluid to generate other reactive oxygen species to enhance local oxidative stress, inflammation and epithelial injury [52]. Approximately 40–60% of inhaled ozone is absorbed in the nasal airways, while the remaining can reach the lower airways by diffusing to more distal surfaces essential for gas exchange [54]. The inhalation of ozone causes respiratory symptoms, decrements in pulmonary function, and increased airway responsiveness to nonspecific stimuli such as methacholine in a dose-dependent manner in a healthy subject and can be explained by the mechanisms of inflammation and epithelial injury [55].

Ozone and nitrogen dioxide modulate airway inflammation, while stimulating the release of inflammatory mediators from the bronchial epithelium in the lower airways [56] (Fig. 3). Ozone dissolves in the epithelial lining fluid of susceptible individuals to produce reactive oxygen species (ROS) and lipid modification. It prompts a dose-dependent increase in intracellular reactive oxygen species (iROS) and epithelial cell permeability [57]. This, in turn, acts on intracellular and cell surface pathways leading to the induction of mRNA to produce inflammatory cytokines, growth factors, and remodeling enzymes. The presence of oxidative stress in the airspaces and the blood initiates a number of early events during pulmonary inflammation [58]. Inflammatory cells are sequestered in pulmonary

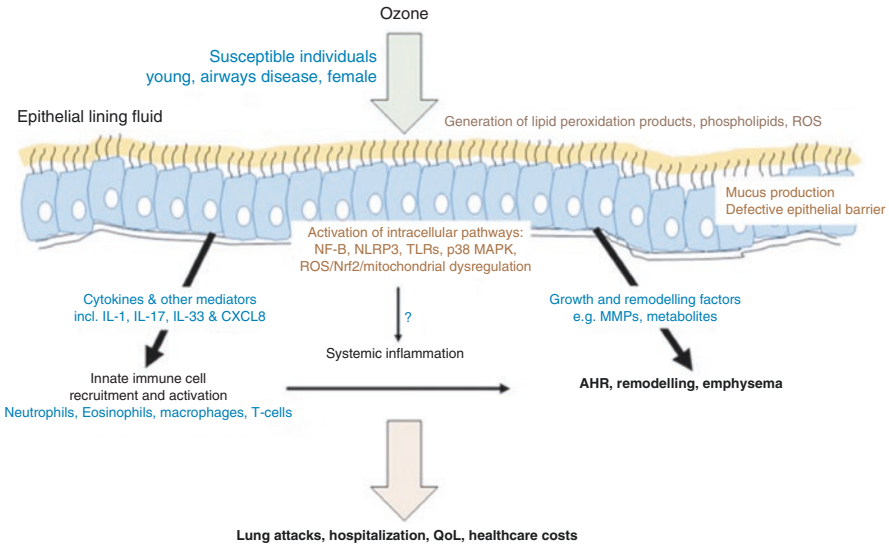

Fig. 3 This image demonstrates the effect of ozone on the epithelial barrier of the lung. Ozone activates intracellular pathways which then activates innate cell recruitment and activation which yields airway hyperresponsiveness, remodeling, and emphysema. (With permissions from Mumby and Chung [52]. License: https://creativecommons.org/licenses/by/4.0/legalcode)

microcirculation and recruited with the generation of mediators such as IL-8, which then activate and generate ROS [59].The ROS upregulates CD 18 integrins and, subsequently, upregulates the NADPH oxidase H_2O_2 generating system [59]. Macrophages, neutrophils, and eosinophils are next activated to generate oxygen radicals which then convert to hydrogen peroxide. In neutrophils, myeloperoxidases catalyze the formation of potent oxidant hypochlorous acid from H_2O_2 [59]. Thus, ROS propagate an inflammatory cascade of oxidative stress.

Amplification of ROS and lung inflammatory events depletes intracellular glutathione (GSH), results in oxidation of membrane phospholipids, and eventually leads to cell death [59]. Oxidants in airways also may induce a secondary release of inflammatory mediators which triggers proliferation and activation of inflammatory signaling pathways leading to severe disease of asthma, COPD, and bronchiectasis [59]. Additionally, in CF and non-CF bronchiectasis, ozone-induced oxidative stress has been found to be enhanced air-liquid interface cultures of the lung which releases IL-8, which is important to the inflammatory cascade [60]. In experimental models, the CF airway epithelium appears to be more vulnerable to inhaled toxins compared to healthy lungs [61]. Extrapolated from this study, one can infer that the airway epithelium of a patient with bronchiectasis is more vulnerable to inhaled toxins such as ozone and nitric oxide.

In addition to animal models, human studies have also demonstrated the effect of ozone on the lungs. In a survey of more than 70,000 children with asthma, study subjects exposed to ozone (50–100 ppd) demonstrated a significant increase in the

release of IL-8, GM-CSF, RANTES, and sICAM-1 after 24 h of incubation of the human bronchial epithelial cells [62]. The increase in inflammatory markers as a result of exposure to ozone demonstrates how ozone stimulates an inflammatory response that can have an effect on airway disease such as asthma, copd, and bronchiectasis in areas of high air pollution. Ozone has a direct impact on the levels of inflammatory mediators in the blood, and subsequently, increased inflammatory mediators in the blood result in increased airway inflammation which is directly or indirectly associated with airway hyper-responsiveness.

Ambient NO_2 is a strong oxidizing and nitrating agent, and it is known to have a deleterious effect on the lungs [63]. High levels of nitric oxide from environmental pollution in the oxidative environment of the airway of people with asthma lead to greater formation of reactive nitrogen species (RNS) and subsequent oxidation and nitration of proteins increases chronic inflammation [64]. Early changes in NO_2 exposed normal human bronchial epithelial cells (NHBE) are causally linked to increased pro-inflammatory mediators such as nitric oxide, interleukin 1β, tumor necrosis factor (TNF) - α and IL-8 [65]. In addition to the inflammatory mediators mentioned, polymorphonuclear monocytes (PMNs) also play an active role in lung inflammation, and NO_2 exposed NHBEs are found to have increased adhesion of PMNs which yields a higher amount of HBEC apoptosis [65]. HBEC apoptosis is also increased in the presence of IL8 and TNF-α and and interferon-ɣ, which correlates with an upregulation of intercellular adhesion molecule-1 (ICAM-1) [65]. ICAM-1 is known for its role in inflammation and intracellular signaling.

Antioxidant Balance Antioxidant balance is essential to maintaining homeostasis with a robust protective response. Environmental oxidants such as ozone cause cellular damage by lipid peroxidation which has the downstream effects of increasing airway responsiveness and reducing pulmonary function in normal subjects. Antioxidants balance these environmental oxidants, and reduced levels of antioxidants have been associated with certain lung conditions such as asthma. The reduced state of glutathione (GSH) has been specifically studied as it has a role in the inflammatory proliferative cascade and is an anti-oxidant which counters the effects of ROS and RNS [58]. Glutathione plays a central role in protection against airway oxidative stress. GSH is a tripeptide comprised of a thiol group, and the oxidation of glutathione (GSSG) reduces the reactive oxidant species (ROS) hydrogen peroxide (H_2O_2) to H_2O via glutathione peroxidase which is protective in an inflammatory state Antioxidant defense pathways and GSH homeostasis are controlled by GSH S- transferase, which is found in high concentrations in the lung [66].

In one observational cross-sectional study during high ozone season in Atlanta, GSH levels were found to be the same between individuals with asthma and healthy controls, but serum albumin was found to be significantly lower in the group with asthma [66]. When controlling for $\%FEV_1$, an increase of 1 g/dL in albumin was associated with a clinically significant higher quality of life score. The non-enzymatic anti-oxidant anti-inflammatory properties of systemic albumin may play a role in maintaining lung function because albumin levels are directly correlated to

lung function and inversely correlated to plasma reduced GSH [66]. Thus, while GSH is important itself, albumin could be a factor in maintaining lung function under periods of oxidative stress and the two factors may be interrelated. The antioxidant albumin is believed to regulate glutathione activity in lung epithelial cells, and the deficiency of albumin likely diminishes an individual's response to oxidant stress, such as with ozone exposure.

Clinical Implications of Traffic Related and Ozone Pollution

Certain individuals and conditions are more vulnerable to the clinical implications of pollution. For instance, the prenatal period and infancy are important windows for the onset of asthma because the strongest effect of TRAP has been observed in relation to exposure from infancy up to 1 year of age [67]. When the mother inhales pollutants during pregnancy, the pollutants can cross the placental barrier, induce oxidative stress, and directly impair the fetus' lung by disturbing organogenesis [68]. Air pollution can also affect the fetus' nutrients and oxygen which can impair birth weight and lung function [68]. The Pollution and Asthma Risk and Infant Study found that TRAP exposure during the second trimester is associated with lower lung function when children become 8 and 9 years of age [68]. The second trimester of pregnancy is a crucial time during which the fetus' respiratory airways are formed and lung morphology significantly develops [68].

In addition to the prenatal effect on the child's lungs, a postnatal effect is also observed. Clinically, a Swedish birth cohort found that there is a modest positive association between air pollution exposure from traffic and the onset of asthma in children during the first 12 years of life [69]. When children were exposed to TRAP exposures early, it was associated with lower FEV_1 and FVC as well as with repeated lower respiratory tract infections [68]. The findings of this same study also suggest that chronic TRAP exposure could be more harmful to the child than early acute TRAP exposure [68]. Once sensitized to TRAP, these children were more vulnerable to early postnatal TRAP exposure, resulting in airway obstruction demonstrated by a lower FEV_1/FVC ratio [68].

With knowledge of these associations, clinicians can have an important role in counseling their patients. Clinicians should be aware that days of high air pollution exposure may cause asthma exacerbations. Individuals with airway diseases such as asthma, COPD and bronchiectasis should be encouraged to minimize their time outdoors during a smog alert; any vigorous exercise outdoors that increases minute ventilation should be avoided when possible [70]. Both acute and chronic TRAP exposure can result in increased hospitalizations and decreased quality of life as well as large healthcare costs for the individual and the society [17]. These vulnerable patients with chronic lung conditions will benefit from counseling to adapt and stay indoors during high exposure days. In children and adults alike, therapeutic approaches that target neutrophilic airways have yet to enter clinical practice. Therefore, individuals with asthma that are affected by TRAP are advised to first

attempt avoidance of TRAP in addition to other lifestyle modifications such as weight loss and smoking cessation. An overlooked opportunity for guidance may also include cautioning pregnant women or young children to avoid high levels TRAP exposure if possible. This can be accomplished by distancing from polluted areas or by wearing a mask [69].

Although the mechanism of non-allergic asthma is different from that of allergic asthma, treatment of TRAP related asthma exacerbations need not differ from the usual clinical practice. Exacerbations on high pollution days can be prevented by maintenance inhaled corticosteroid therapy. Inhaled corticosteroids have been shown to reduce oxidative stress and improve airway function and asthma symptoms in patients with TRAP exposure [26]. Treating upper airway inflammation (e.g. rhinitis or chronic rhinosinusitis) in these patients should also be beneficial. As suggested earlier, individuals should seek information regarding air quality to guide route and timing of outdoor exposure. Even crossing over to a less polluted side of the road can lead to 18% reduction in exposure to $PM_{2.5}$, and optimize time in proximity to green spaces away from major traffic intersections [71]. Green space could lower a child's asthma risk by potentially decreasing the effects of heavy traffic [72]. In a cross- sectional study of 4447 children aged 6–7 years old in Australian, children who exposed to high traffic volumes and areas with 0–20% green space quantity, the odds ratio of affirmative asthma was 1.87 (95% CI 1.37–2.55) [72]. When participants lived in an area with over 40% green space coverage, the association between heavy traffic and asthma was significantly lower with and odds ratio of 0.32 (95% CI 0.12–0.84) [72].

Public Health and Prevention

Public Policy: Past Air pollution has been associated with important adverse health effects, including a significant increase in mortality [71]. Several historic air pollution events such as the Meuse Valley Fog of 1930, Donora death fog in 1948 and London Fog in 1952 led to thousands of deaths [73]. The Meuse Valley Fog of 1930 in Belgium, a heavily industrialized area in Europe, is the first scientific proof of the potential for atmospheric air pollution causing death and disease [73]. Between December 1 and December 5 of 1930, a thick fog of air pollution descended on hundreds of people of Meuse Valley, causing these people to have severe respiratory signs and symptoms with more than sixty people dying over the next 3 days [73]. The official committee's report states that the people during the fog had "dyspneic breathing characterized by paroxysms and slowed expiration, like asthma" [73]. In the investigation to determine the culprit of the fog, the committee identified thirty substances caused by twenty-seven factories which included irritant gases and fine soot particles [73]. This disaster led the Belgian government to propose improvements to the monitoring of air pollution. However, at that time, little was done as air pollution was considered a consequence of prosperity, and it was not believed that air pollution could influence chronic disease. This was the first point

in history when air pollution was clearly to blame for deleterious effects on acute respiratory health and mortality.

In 1948, a smog descended among the residents of the Donora, Pennsylvania township which relied on two major industrial plants for their livelihood, the American Steel and Wire plant and the Donora Zinc Works [74]. The smog brought about increasing numbers of reports of respiratory distress within the town. Within days, twenty individuals had died within Donora and Webster Pennsylvania. Serious illness affected 1440 individuals and 4470 individuals had notable symptoms, together comprising half the population of Donora [74]. The United Steelworkers Union, the state of Pennsylvania, and the American Steel and Wire asked the United States Public Health Service to investigate the smog, and this became the first time the United States had a large-scale epidemiological study of an environmental health disaster [72]. The investigators of the incident concluded that the air pollution (heavily particulate matter) was caused by the American Steel and Wire plant as well as the Donora Zinc Works which covered much of the riverfront property. The investigators did not identify a single contaminant during the smog, and highlighted numerous contributing factors. In 1950, the American Journal of Public Health published an editorial which remarked on how the air pollution caused a higher death rate of non-Whites compared to Whites [75].

The year 1952 brought to the forefront a new public health disaster called the London fog which was a result of factory related air pollution, specifically particulate matter. In October 30, 1952, seventeen people died due to air pollution, followed by three more later that week [76]. Mortality rates from December 1952 to February 1953 were 50–300% higher compared to the previous year [76]. Children born in London around the time of the Great Smog experienced a much higher rate of self-reported asthma compared to children not born in London during the same time [77]. With the death rate from the London Fog so high, this episode is viewed as a catalyst for the study of air pollution epidemiology.

Incidents such as these led to the development of the U.S. federal law: Clean Air Act of 1970, which was later revised in 1990. The Clean Air Act (CAA) gave the Environmental Protection Agency (EPA) the authority and oversight needed to take effective action to fight environmental pollution. The purpose of the Clean Air Act has been to prevent air pollution, protect the ozone layer and to promote public health [78]. The EPA created the National Ambient Air Quality Standards (NAAQS) to monitor the six pollutants, one of which is particulate matter [79].

Public Policy: Present and Future It is evident that poor air quality plays a role in lung health, and particularly in asthma. Epidemiologic, laboratory exposure studies, as well as mechanistic studies on the pathophysiology of TRAP explain how air pollution increases oxidative stress and enhances inflammatory and allergic activity in the airways. These effects lead to significant morbidity among those who are the most vulnerable due to age, medical comorbidities, lower socioeconomic status and other disparate social determinants of health. In addition to our understanding of

how to reduce the effects of these pollutants, it is imperative that we address the root cause of these exposures so that we can improve air quality for all individuals.

Roadways are important features of the environment in the United States, and trucks and automobiles are responsible for most urban air pollution. With ongoing environmental regulations, the tail pipe exhaust component of $PM_{2.5}$ emissions has decreased over time. Reductions in ambient $PM_{2.5}$ have been shown to be consistent with longer life expectancies [7] . Studies to date demonstrate the benefit of particulate matter reductions are greater in urban areas than in rural areas [7]. However, rural area are understudied. Stringent policies need to be in place to control particulate matter levels in rural and urban regions.

Since motor vehicle emissions and power plants are the main sources of both primary and secondary pollutants in developed countries, cleaner vehicle and energy production that do not rely on combustion of fossil fuels are necessary to better air quality [12]. Policy initiatives should incentivize alternatively powered vehicles and renewable electricity. Additionally, existing vehicle traffic should be curtailed in growing cities and developed cities by enforcing parking restrictions, vehicle free zones and closing off roads to traffic [12]. An effort spanning all nations can make achieving a reduction in air pollution and a reversing climate change a realistic possibility.

Climate change is playing a role in the global rise in the prevalence and severity of airway disease [80]. With industrialization and the world-wide increase in the number of motor vehicles, there is an abundant amount of TRAP pollution which includes mixtures of PM, nitrogen oxides, and ozone among other gases. Increased transportation increases the environment's nitrogen dioxide which then participates in forming ground level ozone levels during periods of high temperatures [80]. Hence, increases in industrialization and thus the amount of pollution with climate change inevitably will cause an increase in the prevalence of airway disease and severity. The increase in heat indirectly affects decomposition of vegetation, soil erosion and wildfires causing an increase in environmental particulate matter [80]. This increase in particulate matter invariably has an effect on the onset and severity of airway disease. Not only does climate change have an effect on progressive warming, but there is also an increase in the unpredictability of weather patterns [81]. Both of these have an effect on airway disease [81]. Worsening air quality and increased allergens attributed to climate change will worsen existing disease [81]. Exposure to climate change and air pollution is linked to signs of obstructive airway disease such as asthma exacerbations measured by increased medication use, visits to the emergency department and hospital admissions [82].

Due to increasing global temperature in the setting of climate change, the use of the air conditioner has increased internationally. While cooling the interior of a building, the device emits carbon dioxide and fine particulate matter while forming ground level ozone outdoors [83]. The increased use of air conditioning in response to a warming climate could result in one thousand additional deaths due to air pollution annually in just the eastern USA by the year 2050 unless alternate

technologies are discovered and used [83]. International organizations such as the Sustainable Energy for All and the International Energy Agency (IEA) are working together to develop solutions to provide more efficient indoor cooling [83]. To avoid the utilization of air conditioning, initiatives include designing buildings with improved insulation and ventilation as well as increasing urban green space among other energy efficient measures [83]. Some evidence suggests that electric fans with light water spraying could be an effective tool against heatwaves [83]. In addition to changes in temperature, climate change also can have an effect on wind patterns and changes in precipitation. Wind circulation increases episodes of long-distance transport of air pollutants, and changes in precipitation patterns can increase the frequency and severity of forest fires [80]. Both phenomena can cause and exacerbation airway disease due to the circulation of air pollution [80].

Summary/Conclusion

Poor air quality /air pollution from traffic sources are associated with adverse health effects. These have been shown in multiple studies, epidemiologic and clinically, and various public policies have helped to improve air quality. Notably, exposure to TRAP and ozone can be associated with new airway disease in addition to exacerbating existing disease, causing morbidity among the population. Mechanisms such as oxidative stress and inflammation create a toxic milieu and perpetuate clinical symptoms of inherent lung conditions. Clinician awareness of TRAP and its clinical downstream effects can translate into the ability to educate a patient and enabling her to take more control over her lung health and environment. The clinician also has the ability to advocate on behalf of public health to improve air quality for all citizens, particularly those who are most vulnerable and less able to shield themselves from this prevalent threat to health. Alternative strategies such as behavioral changes, improved air quality monitoring and accountability from sources (combustion and non-combustion), and newer technologies for climate change mitigation and air quality improvement with scientific advancements are parts of a larger goal to improve the air quality and reduce climate-related factors to overall and lung health.

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Environmental Factors on Lung Health in Cystic Fibrosis and Non-cystic Fibrosis Bronchiectasis

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Introduction

Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive disease in the United States with an incidence of approximately 1 in 4000 [1]. CF disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that encodes for an epithelial chloride channel. Mutations in *CFTR* lead to dysfunctional, fewer numbers, or complete absence of functional CFTR epithelial chloride channels leading to multi-organ dysfunction. In the lungs, CF disease causes a dehydrated airway surface liquid leading to chronic infection, inflammation, bronchiectasis and progressive loss of lung function with the majority of deaths caused by respiratory failure [1]. The clinical course of CF pulmonary disease is heterogeneous even between individuals with the same CFTR mutations. This disconnect often observed between the genotype and phenotype cannot be fully explained by well-defined poor prognostic indicators such as female sex, low BMI, race and ethnicity, bacterial colonization in the respiratory tract with *Pseudomonas aeruginosa* and *Burkholderia cepacia*, and low socioeconomic status [2–7]. Genetic modifiers in genes other than CFTR have been implicated in contributing to this heterogeneity as have environmental factors such as exposure to secondhand smoke, indoor mold, fine particulate matter (PM), ozone (O_3), and ultrafine (UF) and nanoparticles (NP) [7].

Bronchiectasis can also occur in other respiratory diseases and is characterized by destruction of the large airways, bronchi and bronchioles resulting in their dilatation and dysfunction of mucociliary clearance. Chronic sputum production and impaired bacterial clearance lead to recurrent respiratory tract infections and a

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progressive decline in lung function and can lead to worse quality of life and contribute to further morbidity [8]. The incidence of non-CF bronchiectasis is 52 patients per 100,000 adults in the US, and the prevalence increases with age [9].

From the time we are conceived, exposure to various factors in our environment can have an effect on our growth, development, and health. The totality of exposures in our environment over our lifetime and how it relates to health is known as the exposome [10, 11]. One of the best studied aspects of the exposome is exposure to air pollution. Studies have shown negative cardiovascular and respiratory effects from long-term exposure to air pollution. The effects of long-term exposure to PM with an aerodynamic diameter of 2.5 μm ($PM_{2.5}$) or less and O_3, even at levels below the National Ambient Air Quality Standards, have been associated with increased mortality [12–14]. The World Health Organization (WHO) estimates seven million people die every year worldwide as a result of exposure to air pollution with low and middle income countries being most affected [15]. Individuals with preexisting lung disease such as CF and non-CF bronchiectasis seem to have an increased susceptibility for negative effects from high concentrations of inhaled air pollutant [16]. In a study of the effect of inhaled NP using CFTR mutant mice, researchers noted higher NP uptake by alveolar epithelial cells and a more exaggerated and prolonged inflammatory response in the CFTR mutant mice as compared to normal controls [17]. Other studies have shown negative effects on lung function, frequency of pulmonary exacerbations, and acquisition of pulmonary infections in people with CF and non-CF bronchiectasis exposed to high levels of air pollutants and will be discussed in the sections to come.

Pathophysiology

The cellular and molecular mechanisms behind the toxic effects of PM on the alveolar epithelial cell (AEC) are complex and seem to involve DNA damage and apoptosis by formation of reactive oxygen species (ROS) and upregulation of the mitochondria-regulated death pathway [18]. Researchers at Stanford University conducted a study to evaluate the effects of PM on CF airway epithelium to determine the exact mechanisms responsible for the toxic effects of PM in CF disease [19]. They used human bronchial epithelial (HBE) cells that expressed F508Δ and W1282X CFTR mutations (named IB3-1) and compared the effects of exposure to $PM_{2.5}$ with HBE cells derived from the IB3-1 cell line with the CFTR mutations corrected (named S9) and normal human bronchial epithelial cells (NHBE). Exposure to $PM_{2.5}$ enhanced apoptosis in IB3-1 cells compared with their controls and the S9 and NHBE cells, and reduced mitochondrial membrane potential ($\Delta\psi m$) and activated caspase-9 and PARP-1 (modulators of the apoptotic pathway) in IB3-1

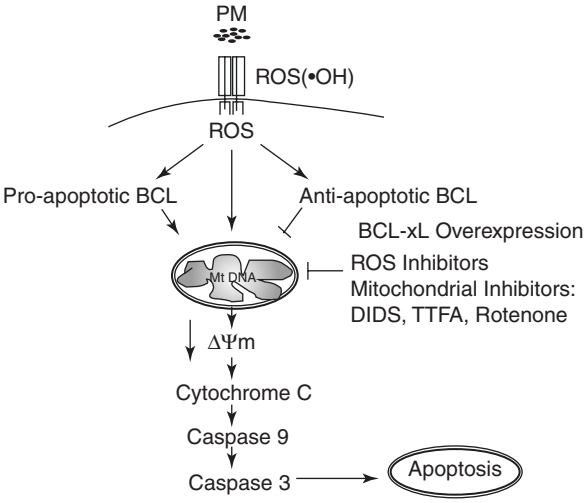

Fig. 1 Schematic diagram detailing the effects of particulate matter in human cystic fibrosis bronchial epithelium from formation of reactive oxygen species and BCL mediated activation of mitochondrial apoptosis by regulating mitochondrial outer membrane permeabilization, reduction in mitochondrial membrane potential (Δψm), and leading to upregulation of proapoptotic mediators. (Republished with permission from Kamdar, O et al [19])

cells compared to S9. $PM_{2.5}$ exposure led to upregulation of proapoptotic mediators while expression of anti-apoptotic mediators remained unchanged (Fig. 1).

The effects of O_3 on CFTR expression have also been studied using in vitro and in vivo bronchial epithelium. Ozone stress decreased transcription of CFTR and CFTR chloride current in human bronchial epithelial cells through a STAT1 signaling pathway [20]. Exposure to O_3 has also been shown to cause increased mitochondrial dysfunction, membrane damage, and apoptosis in CF airway epithelial cells as compared to non-CF airway epithelial cells. One of the mechanisms by which this occurs is by the under expression of SERCA2, a regulator of calcium signaling, in CF epithelium leading to increased production of pro-inflammatory mediators particularly NF-κB [21].

Similar mechanisms likely also take place in the airways of people with non-CF bronchiectasis in response to exposure to air pollutants. Other proposed mechanisms for lung injury and inflammation by exposure to air pollutants in respiratory disease involve an inflammatory response induced by free oxygen radicals and an impaired cellular immunity by suppressing macrophage function leading to the destruction of the airway epithelial barrier and lung parenchyma [22]. The inflammatory response in the alveolar cells caused by exposure to ambient PM also involves activation of the epidermal growth factor receptor (EGFR) signaling pathway leading to the increased release of pro-inflammatory cytokines [23, 24].

Effects of Air Pollution on Lung Function and Pulmonary Exacerbation in CF

The negative effects of exposure to air pollution likely starts even before we are born. Studies have shown exposure to certain air pollutants during the prenatal period has a negative effect on lung function and development during childhood and increases risk of respiratory symptoms such as wheezing [25]. Studies in infants diagnosed with CF revealed increased markers of inflammation including neutrophil count, neutrophil elastase (NE) activity, and level of interleukin-8 in bronchoalveolar lavage fluid (BALF) as compared with newborn controls even in the absence of identifiable pulmonary infection [26]. This suggests that infants with CF already have heightened levels of airway inflammation shortly after birth. It is unclear what role prenatal exposure to air pollution has on airway inflammation, lung function, and development in infants with CF but certainly this population is at risk for negative effects as has been shown in larger studies in the general population.

Pulmonary exacerbations in CF contribute to a perceived worse quality of life, missed work or school, and may result in permanent loss of lung function and shortened survival [27]. There is growing evidence to suggest exposure to high levels of air pollution may lead to increased frequency of CF pulmonary exacerbations and decreased lung function. Investigators at the University of Washington used data from the Cystic Fibrosis Foundation National Patient Registry (CFFNPR), a large data set of people with CF in the United States, in 1999 and 2000 to assess whether exposure to PM with an aerodynamic diameter of 10 μm (PM_{10}) or less, $PM_{2.5}$, and O_3 was associated with a decline in lung function and more frequent pulmonary exacerbations [28]. Air pollution values from the Aerometric Information Retrieval System from that same time was linked to the home zip codes of the individuals from the CFFNPR. Increases of 10 μg/m^3 in PM_{10} or $PM_{2.5}$ were associated with an 8% and 21% increased odds respectively of two or more pulmonary exacerbations, and for every increase of 10 μg/m^3 in $PM_{2.5}$ there was an associated fall in lung function of 24 ml as measured by FEV_1. Increases in exposure to O_3 of at least 10-ppb was associated with a 10% increase in odds of two or more pulmonary exacerbations.

Other studies have noted similar findings. At the Children's Institute, Clinics Hospital, University of São Paulo, Brazil, an observational study was performed between 2006 and 2007 to examine the effects of air pollutants (PM_{10}, sulfur dioxide [SO_2], carbon monoxide [CO], nitrogen dioxide [NO_2], and O_3) on the risk of CF pulmonary exacerbation [29]. A total of 103 children and adolescents with CF were seen. Data on the daily concentrations of air pollutants were obtained from the São Paulo State Environmental Agency. Their analysis showed that increases in ozone was associated with an increase in the risk of CF pulmonary exacerbation 2 days after exposure. No other air pollutants studied were associated with a statistically significant increased risk of CF pulmonary exacerbation.

At Children's Hospital Los Angeles (CHLA), a retrospective study was performed to evaluate the effect of air pollutant levels and geographic proximity to

major roadways on the frequency of exacerbations in the CF patients at their care center [30]. Their study showed an association between living in close proximity with major arterial roads and an increase in frequency of CF pulmonary exacerbations.

In a case-crossover analysis of 215 patients with CF between years 1998–2010, investigators studied the effect of PM_{10}, ozone, and NO_2 on CF pulmonary exacerbations [31]. Levels of these pollutants were measured on the day of exacerbation and on the 2 days prior to the exacerbation. They noted an increase in risk of CF pulmonary exacerbation associated with elevated levels of PM_{10}, NO_2, and ozone on the day of exacerbation and elevated levels of NO_2 on the day before exacerbation.

Effects of Air Pollution on Acquisition of Pulmonary Infections

CF is characterized by chronic respiratory infections resulting in chronic inflammation, development of bronchiectasis, progressive obstructive lung disease, and loss of life-years [1]. Acquisition of certain microorganisms such as *Pseudomonas aeruginosa* (*Pa*) and *Staphylococcus aureus* (*Sa*) to the CF respiratory microbiome often occurs at a very early age. *Pa* respiratory infection in CF is a predictor of increased morbidity and mortality with studies showing increased risk of death, lower lung function, lower BMI, and increased risk of pulmonary exacerbation [32]. Using data obtained from the CFFNPR and the U.S. Environmental Protection Agency Air Quality System, a retrospective study was performed to determine the effect of exposure to higher levels of $PM_{2.5}$ on initial acquisition of *Pa* in U.S. children 6 years of age and younger [33]. Results showed that exposure to higher levels of $PM_{2.5}$ was associated with increased risk of *Pa* acquisition. A similar study done by the same group was performed to determine the effect of exposure to higher levels of $PM_{2.5}$ on initial acquisition of methicillin susceptible and methicillin resistant *Staphylococcus aureus* (MSSA and MRSA), *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans* in U.S. children 6 years of age and younger [34]. Children exposed higher levels of $PM_{2.5}$ had significantly increased risk of MRSA acquisition, but not any of the other tested microorganisms.

Effects of Indoor Mold Exposure

Individuals with CF are at risk for developing allergic bronchopulmonary aspergillosis (ABPA). ABPA is an allergic lung disease caused by Th2 response to *Aspergillus fumigatus* and affects between 7% and 9% of people with CF [35]. *A. fumigatus* is a mold found worldwide in both outdoor and indoor air and has been shown to colonize up to 57% of individuals with CF [36]. Despite the prevalence

and morbidity associated with ABPA, there is surprisingly little data on the effects of indoor mold exposure on the development of ABPA. A pilot study done by Rocchi et al [37] aimed to determine whether indoor exposure to *A. fumigatus* was associated with ABPA diagnosis. To study this, they placed electrostatic dust fall collectors (EDCs) in the homes of adults with CF who either were diagnosed with ABPA, had positive serum precipitins for *A. fumigatus* but did not meet criteria for ABPA, or did not have either a diagnosis of ABPA or serum precipitins positive for *A. fumigatus*. Samples were then collected and culture and qPCR were performed. Results showed DNA concentrations of *A. fumigatus* were significantly higher in the homes of ABPA patients, suggesting that indoor exposure to *A. fumigatus* may increase risk of developing ABPA. Another study done by Sapet et al. [38] showed no association between the presence and density of *A. fumigatus* in the homes of children with CF and airway colonization by *A. fumigatus*, though there is little association between airway colonization and diagnosis of ABPA [39]. Larger studies are needed to determine if indoor exposure to *A. fumigatus* is a significant risk factor for development of ABPA.

Secondhand Smoke (SHS) Exposure on Lung Health in CF

Exposure to tobacco smoke both indirectly during prenatal development and through second and thirdhand smoke during postnatal development is associated with multiple negative health consequences including an increase in the frequency of wheezing and lower respiratory tract infections, reduced lung function, and an increased risk in sudden infant death syndrome (SIDS) [40]. Given the deleterious effects of SHS exposure on young children and the susceptibility of children with CF for respiratory illness, considerable interest has been given to studying the effects of SHS in children with CF. According to the 2019 Cystic Fibrosis Foundation Annual Data Report, 15.3% of people with CF in the U.S. reported at least monthly exposure to tobacco smoke, and 1.9% of people with CF admitted to being active smokers.

The negative health effects of exposure to tobacco smoke seem to start early in development. Smoking by mothers during pregnancy has been associated with significantly lower lung function in young children with CF [41]. In a mouse model of mucociliary obstructive lung disease, exposure to postnatal SHS resulted in failure to clear respiratory bacterial infection, thought to be the result of impaired neutrophil recruitment and *TH2* response [42]. In 2008 as part of the US Cystic Fibrosis Twin and Sibling Study (CFTSS), investigators found that exposure to SHS was associated with significantly lower FEV_1 and that genetic variations in *CFTR* and the CF-modifier gene *TGFβ1* were associated with a greater decline in lung function in those exposed to SHS [43]. A small observational study of SHS exposure and lung function in CF found an association between a decrease in FEV_1 and FVC of 4% and 3% respectively for every 10 cigarettes smoked in the household per day [44]. Other studies in children with CF have found association between SHS

exposure and other pulmonary function testing abnormalities including increased bronchodilator responsiveness and air trapping and a greater likelihood to culture MRSA and anaerobic bacteria on respiratory culture [45, 46].

Exposure to SHS also appears to have detrimental effects on CFTR function. Using an in vitro model of human bronchial epithelial cells (HBEs) expressing wild-type CFTR, investigators at the University of Alabama showed that exposure to SHS caused decreased chloride ion transport by CFTR. The same group then used a murine model expressing wild-type CFTR and exposed these mice to either SHS or ambient room air. They then evaluated CFTR function by measuring nasal potential difference (NPD) in these mice. Their results showed a 52% decrease in CFTR function in mice exposed to SHS compared to controls [47]. CFTR modulators are a new class of drug for individuals with CF that act directly on the CFTR epithelial membrane protein to improve chloride transport and have been shown to improve FEV_1, BMI, quality of life scores, and reduce hospitalizations and CF pulmonary exacerbations [48, 49]. In a recent retrospective study using data from the CFFNPR, investigators compared lung function before and after initiation of Tezacaftor-Ivacaftor (TEZ-IVA, CFTR modulator) in smoke-exposed and unexposed pediatric CF patients age ≥12 years. Smoke-exposed individuals started on TEZ-IVA had an 8% lower baseline percent predicted FEV_1 ($ppFEV_1$) and experienced a greater decline in lung function over the study period compared with unexposed individuals started on TEZ-IVA. TEZ-IVA use was associated with an improvement in $ppFEV_1$ in unexposed individuals, but did not result in an improvement in lung function for those that were smoke-exposed suggesting that SHS exposure diminishes the therapeutic benefit of TEZ-IVA in individuals with CF [50].

Effects of Rising Temperature and Climate Change on Lung Health in CF

The earth's climate is undergoing substantial warming largely due to human influence of greenhouse gas (GHG) emissions. Atmospheric concentrations of these GHGs including carbon dioxide, methane, and nitrous oxide are the highest they have been in over 800,000 years and have led to increases in the globally averaged combined land and ocean surface temperature, sea level rise, and loss of snow and ice [51]. According to recent data from the Copernicus Climate Change Service (C3S) as part of the Copernicus Earth Observation Programme of the European Union, the global average temperature is 1.25 degrees Celsius warmer than from pre-industrial time in the 1850's with the two warmest years on record being in the past 5 years (2016 and 2020). Rising temperatures as a result of climate change may also have detrimental health effects on the lung health of the general population and susceptible populations such as individuals with CF.

Spirometry data from two National Health and Nutrition Examination Survey (NHANES) periods (NHANES III from 1988–1994 and NHANES 2007–2012) and

data on the mean annual ambient temperature were studied for associations between lung function and ambient temperature. There was a decrease of 0.71% and 0.59% in predicted FEV_1 for every 10 degrees Fahrenheit increase in mean temperature in NHANES III and NHANES 2007–2012 respectively [52]. These same investigators used data collected on specific environmental factors and subjects enrolled in the CFTSS to study associations between temperature and CF lung disease and infections. Warmer temperature was associated with presence of *P. aeruginosa* and lower lung function in subjects from the CFTSS. These associations were replicated in other data sets including the U.S. CF Foundation Patient Registry (CFFPR) and the Australian CF Data Registry and in prospectively obtained subjects in Australia/New Zealand [53]. A follow up study showed that this association between temperature and lung function were largely mediated by three respiratory pathogens: *P. aeruginosa*, mucoid *P. aeruginosa*, and MRSA in both the CFTSS and U.S. CFFPR [54].

Effects of Air Pollution on Lung Function and Pulmonary Exacerbation in Non-CF Bronchiectasis

Exposure to high concentrations of air pollutants can increase risk of respiratory disease particularly in those with pre-existing lung disease. A study done in Eastern China in 2013 and 2014 found that increased concentrations of PM, NO_2, and SO_2 were associated with increased emergency room visits for upper respiratory tract infections and pneumonias in the general population [55]. Similarly, a study done in Central Arkansas showed air pollutants $PM_{2.5}$and O_3 were associated with increased emergency room visits for respiratory diseases [56]. Exacerbations of non-CF bronchiectasis are associated with accelerated disease progression leading to a decline in lung function and increased morbidity and mortality. A study done by Martinez-Garcia *et al* showed that patients with non-CF bronchiectasis who have more than 1.5 exacerbations per year are at risk of faster decline in FEV_1 compared to those who have fewer exacerbations [8]. In a prospective observational cohort study, patients with non-CF bronchiectasis who had greater decrease in peak expiratory flow rate (PEFR) at exacerbation onset were found to have more symptom burden and prolonged recovery [57]. In the same study, there was more than 10% reduction in the PEFR during those exacerbations.

A study done in Ontario, Canada showed that there was positive association between exposure to ambient air pollutants and emergency room visits in patients with chronic pulmonary diseases including bronchiectasis even when pollutant concentration was relatively low [58]. In another study in China, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO had a positive association with outpatient visits for acute exacerbation of bronchiectasis [59]. In a retrospective observational study conducted in Badalona, Spain, Garcia-Olivé *et al* looked at the number of daily hospital admissions and emergency room visits related to exacerbation of bronchiectasis between 2008 and

2016. In this study, there was a significant association between SO_2 levels and an increase in the number of hospitalizations in patients with bronchiectasis. Also, there was a correlation between the number of emergency room visits for bronchiectasis exacerbations and higher SO_2 levels [60]. In a study performed by Geominne *et al* at the University Hospital of Leuven, Belgium, between June 2006 and October 2012, investigators followed 183 adult patients with non-CF bronchiectasis. Patients who were living near a major road were found to have an increased mortality with a HR of 0.28 (CI 95% 0.10–0.77; $p = 0.013$). This was the first study to document that traffic related pollution on patients with non-CF bronchiectasis was associated with increased mortality [61].

Carbon monoxide (CO) is a ubiquitous ambient gaseous pollutant produced by incomplete combustion of traffic related fossil fuels; thus, its concentration and emissions have been regulated by many countries. CO is thought to contribute to the development of inflammatory airway diseases [62]. Ambient CO was associated with all-cause mortality in the China Air Pollution and Health Effects Study (CAPES) [63]. Y. Zhao et al. reviewed the numbers of daily outpatient visits in Dongguan, China for respiratory diseases and correlated them with air pollution data. They found out that ambient CO is associated with increased risk of outpatient visits for all respiratory diseases including bronchiectasis especially in females and in elderly population [64].

Exposure to Arsenic and Bronchiectasis

Many people over the world are exposed to arsenic, a natural element in the earth's crust, through drinking water, particularly in developing countries. Arsenic is associated with multiple diseases including cancer and non-cancer illnesses involving cardiovascular, respiratory, reproductive, and neurologic disease [65]. In a city in Northern Chile, where public water systems are the only source of drinking water, people who were exposed at an early age of life to arsenic were found to have increased mortality from bronchiectasis 30–40 years after the exposure [65].

Summary

Over the course of our lifetime, exposures in our environment affect our growth, development, and health, and the totality of these exposures is known as the exposome. Environmental exposures from air pollution have a negative impact on respiratory health and contribute to both morbidity and mortality. In certain susceptible populations such as those with CF and non-CF bronchiectasis, exposure to air pollution is associated with lower lung function and increased frequency of pulmonary exacerbation and may contribute to acquisition of certain respiratory bacterial infections including *Pa* and MRSA. Indoor exposure to *A. fumigatus* may lead to

increased risk of developing ABPA in CF, though more studies are needed to confirm this finding. SHS exposure is associated with multiple negative health consequences including an increase in the frequency of wheezing and lower respiratory tract infections, reduced lung function, and an increased risk in sudden infant death syndrome (SIDS). In people with CF, SHS exposure may result in failure to clear respiratory tract infections, a faster decline in FEV_1, and can result in decreased function of CFTR, mitigating the potential therapeutic effects of CFTR modulators. As the earth's global average temperature rises as a result of climate change, detrimental health effects may develop as a result. Warmer temperatures have been associated with lower FEV_1 and increased prevalence of *Pa* in respiratory cultures in people with CF. In countries where arsenic is found in drinking water, exposure early in life is associated with an increase in mortality 30–40 years later from bronchiectasis. Environmental exposures are considered modifiable risk factors in chronic lung diseases. With this knowledge, it is our responsibility as clinicians to raise awareness about the effects of air pollutants and support measures that would limit environmental exposures to protect the health of the general population and those individuals that are most susceptible.

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Molds and Respiratory Disease

John McDonnell and Mark Aronica

Introduction

The purpose of this article is to reacquaint the reader with basic concepts relating to the effect of molds on respiratory disease. A framework for understanding will be built by a review of basic fungal biology, followed by exploration of the ways these organisms affect human health. Particular attention will be paid to how molds play into atopic diseases like allergic rhinitis, allergic asthma, allergic bronchopulmonary pulmonary aspergillosis (ABPA), allergic fungal rhinosinusitis, and hypersensitivity pneumonitis. Additionally, the putative role of fungal mycotoxins in speculative disease processes like "toxic mold syndrome" and related "sick building syndrome" will be explored.

Basics

Before discussing how fungi affect human disease, it is useful to review some basic scientific facts on the subject. Fungi are eukaryotes, possessing nuclei enclosed by a nuclear envelope. There are over 140,000 separate species of fungi [1] composing their own scientific kingdom, the vast majority of which do not cause human disease of any sort. Fungi can exist in unicellular (yeast) or multicellular (mold) forms. The former grow by budding, and the latter use filamentous extensions called hyphae which coalesce to form mycelia. Some fungi are dimorphic and can grow either way depending on the constraints of their external environments [2].

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Most molds live in balance with humans and rarely cause negative health effects. However, in an immunosuppressed host, even a normally benign commensal fungus like *C. albicans* can cause severe and invasive disease [2]. In the case of atopic individuals, the failure of immune tolerance to certain fungi can cause or exacerbate a host of problems. In many individuals, the difference between immune tolerance and immune hyperresponsiveness comes down to fungal load – "the dose makes the poison" as the sixteenth century physician Paracelsus famously once said.

Fungi reproduce by making spores via either sexual or asexual processes, and they generate energy by the degradation and subsequent absorption of the world outside them [1]. They are ubiquitous in the environment, but found particularly in places with the correct balance of carbohydrate sources, moisture, and warmth [3]. The environment most favorable to their growth is usually found outdoors (in fact, most fungi found indoors were actually translocated there from the outside). However, under the right conditions, molds can indeed independently grow inside homes [3]. The musty odor associated with such places, due to volatile compounds produced by the fungus, serves as a low-tech but useful indicator of potentially problematic mold growth [3].

Fungi use mycotoxins (low-molecular weight organic chemicals) to kill off microorganism competitors in the immediate environment, enabling them to better obtain micronutrients. Though there is a great deal of public fear regarding these chemicals, the effects on human health are negligible at the minute concentrations normally encountered in the environment [3]. However, in agricultural settings, mycotoxin contamination of food sources can cause population health problems. All crops and cereals can potentially be contaminated under the right conditions of humidity, but the most commonly affected is corn [4]. Although hundreds of mycotoxins have been identified, only six are commonly implicated in agricultural disease: aflatoxins, ochratoxins, fumonisins, patulin, zearalenone, and tricothecenes [4]. These toxins can cause problems such as hepatitis/liver cancer/cirrhosis (aflatoxins), nephrotoxicity (ochratoxins), gastrointestinal disorders (fumonisins), hemorrhage and convulsions (tricothecenes), among others [5].

A curious example, now largely relegated to the medical history books, is found in "Saint Anthony's Fire" or gangrenous ergotism. Ergot is the alkaloid-containing product of the grain fungus *Claviceps purpurea* [6]. Frequent epidemics of ergotism due to contaminated rye bread occurred in the Middle Ages [7]. Ergotism was characterized by limb gangrene ("Saint Anthony's Fire"), convulsions associated with mania and hallucinations (owing to some ergot components with structural similarity to LSD), or sometimes both simultaneously in the particularly unlucky patient [6]. The disorder was featured prominently in medieval art [7] and while it is largely now of historical interest, ergot alkaloids are still occasionally used in medical settings, for example, ergometrine for the treatment of postpartum hemorrhage [6].

Molds and Allergic Rhinitis

Allergic rhinitis is a common problem, affecting approximately 20% of adults and children in the United States [8], and is due to IgE-mediated hypersensitivity to aeroallergens. Broad classes of such aeroallergens include grasses, weeds, trees, animal dander, molds, and dust mites. Classic presenting symptoms include congestion, nasal discharge, sneezing, and facial pruritis [9]. Notably, not all rhinitis is allergic in nature, and definitive discrimination between allergic and nonallergic rhinitis requires assessment of allergen-specific IgE, whether by skin testing or serum testing. Nonallergic rhinitis is more common in older patients, is associated with negative IgE testing, and comprises inflammatory (nonallergic rhinitis with eosinophilia syndrome [NARES]) and noninflammatory (vasomotor, irritant, gustatory) subtypes.

Although in this discussion we are primarily concerned with allergic rhinitis secondary to fungal sensitization, it is worth noting that in high enough concentrations, fungi can have an irritating effect on the nose in the absence of IgE sensitization. This phenomenon is also experienced with other allergens, exemplified by patients with negative allergy testing but persistent symptoms of sneezing and itching in association with, for instance, mowing the lawn. Such patients are certainly symptomatic and often confused when their allergy testing is negative, but the mechanism of their symptoms is due to nasal irritation rather than allergic sensitization. This phenomenon is a subset of nonallergic rhinitis, and is most commonly triggered by respiratory irritants like cigarette smoke, fumes, strong scents [10], and weather changes [11].

When the clinician is concerned for allergic rhinitis due to molds, allergy testing is usually performed to evaluate for sensitization to relevant molds. Percutaneous testing done in the allergy clinic is done by skin prick testing and/or intradermal testing. Skin prick testing involves placing a small drop of allergen extract on a patient's skin and gently pricking, followed by a period of observation (<30 minutes). A significant test result to a given allergen is demonstrated by a wheal and flare reaction. Intradermal skin testing involves injecting a small bleb of allergen intradermally. While intradermal testing is more sensitive, the sensitivity comes at the expense of increased false-positive reactions [12]. An alternative to percutaneous testing is serum IgE testing, in which immunoassays are performed for allergen-specific IgE on a blood sample. This is the preferred method for situations in which the skin cannot be tested, such as in patients with dermatographism, active eczema, or recent antihistamine use.

There are a wide variety of extracts used for percutaneous testing, some standardized and others less so. Most fungal extracts used in allergy testing fall into the latter category, with a significant degree of variability between manufacturers or even in batches from the same manufacturer [3]. Theoretically, a patient may be sensitized to an almost limitless number of different mold species, the vast majority

of which do not have available allergy testing. Happily, from an epidemiologic perspective, most patients with symptomatic fungal allergic rhinitis react to at least one of the three common aeroallergens *Alternaria, Cladosporium,* or *Aspergillus* [3]. Practically, therefore, the clinician can confine routine testing to these three major categories, with more expansive mold testing reserved for special situations [3]. In the use of intradermal testing for specific molds, practices vary, but the practical performance of mold intradermal testing is generally considered poor, and most allergists find that skin prick and/or serum-specific IgE testing is sufficient for the diagnostic workup [13]. If a patient has evidence of IgE-sensitization to a relevant mold, and the sensitization pattern fits with the patient's clinical presentation, he or she would meet criteria for the diagnosis of allergic rhinitis due to mold.

It is important to remember that levels of indoor fungi will generally correlate proportionally with levels of outdoor fungi [14], and there is considerable overlap between the groups. Common fungal species found indoors include *Cladosporium, Penicillium, Aspergillus, Alternaria,* and *Aureobasidium* [14], but these species are also often found outdoors. The physical action of wind blowing outdoor materials indoors, or the translocation of such materials on clothing, is important in understanding this context. With these facts in mind, it is perhaps not as helpful in most situations to attempt a clear division between indoor and outdoor molds.

There is some debate about the degree to which fungal allergy contributes to overall symptom burden in the larger patient population [14]. This stands in contrast to the role of fungal allergens in the pathophysiology of allergic asthma (discussed below), which is well-described. However, it is at least certain that *some* patients are sensitized to molds and that this sensitization can lead to relevant nasal symptoms [15]. The degree of clinical severity likely follows a dose-effect curve, with patients receiving a "higher dose" of molds, such as those in damper environments (old buildings, basements, habitations with standing water), at higher risk for symptoms.

If a specific determination of indoor mold burden is required (an uncommon situation in most practices), a variety of methods are available. The most commonly used is viable mold spore assessment from dust samples, although techniques such as immunoenzymetric assays are available for quantification of select molds that are infrequently detected by the former [16]. With the tremendous variability in mold sampling methods [14], lack of standardized approach to such sampling, and lack of clear reference standards for the interpretation of results, clinicians would do well to remember that "reports on atmospheric fungal spores *always give incomplete information*" (italics added) [14]. Factors that improve assessments include comparison of indoor samples to the proximal outdoors and avoiding assessments of fungi from areas of the building not exposed to air (situations where respiratory contact would be implausible). Even with these measures, clinicians should avoid putting too much faith in these assays or ascribing particular significance to testing results.

As the severity of allergic rhinitis varies from patient to patient, treatment options abound. At the most basic level, the optimal treatment is always allergen avoidance. For molds, such avoidance would necessitate careful attention to dampness,

including prevention and/or immediate remediation of water damage in the patient's environment, as well as taking general measures to decrease influx of outdoor allergens to the indoor environment. Pharmacotherapy is the mainstay of the next level of treatment, and the safest and most efficacious class of medications for allergic rhinitis are undoubtedly the nasal corticosteroids [17]. For patients who do not want to take nasal corticosteroids, or whose symptoms do not improve, other medication options include oral antihistamines, nasal antihistamines, mast cell stabilizers, leukotriene antagonists, and sympathomimetics. On the more severe end of the spectrum, or in the case of patients who dislike taking regular allergy medications, the final treatment option is allergen immunotherapy. Such therapy involves giving subcutaneous injections of escalating doses of specific allergens over a period of years, with the goal of achieving a desensitized state. In some patients, this desensitized state can persist for decades after therapy is complete, although not all patients respond this well.

Downsides to allergen immunotherapy include the pain of injection, common local reactions, cost, and the time commitment for the patient. There is also a small risk of anaphylaxis associated with the therapy, and most practices require in-office injections with a period of observation after each shot, with some also requiring the patient carry a personal epinephrine source on shot days. While other allergens have formulations for immunotherapy that can be given through the sublingual route, there is no such option for mold-allergic patients.

Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is one of three subtypes of chronic rhinosinusitis, which is defined by the presence of sinus and nasal inflammation for at least 12 weeks. The other two subtypes (chronic rhinosinusitis with polyps and chronic rhinosinusitis without polyps) are not triggered by fungal exposure and thus will not be addressed here, although they comprise a majority of chronic rhinosinusitis cases (90–95%) [18].

AFRS is a disease predominantly afflicting young adults (average age at diagnosis 22 years) living in humid climates such as the Mississippi basin [18]. The pathophysiology is thought to involve trapping of fungal spores in a healthy host with subsequent IgE-sensitization to the mold. This is followed by local growth of the mold in the nose and sinuses, triggering a downstream Th2 response, characterized by production of IL-5, IL-13, and chronic eosinophilic inflammation [19] that can ultimately lead to airway remodeling.

The most widely accepted diagnostic criteria, from Bent and Kuhn, require (1) IgE-mediated hypersensitivity, (2) nasal polyposis, (3) characteristic CT findings, (4) eosinophilic mucous without fungal invasion, and (5) positive fungal stain [20]. The CT findings can vary, but include hyperdensities in the opacified sinuses (corresponding to eosinophilic mucin), sinus cavity expansion, bone demineralization,

and bony erosion [21]. Commonly implicated fungi in AFRS include *Bipolaris*, *Curvularia*, and *Aspergillus* [22], although *Alternaria* species are sometimes involved as well [14].

An important point to reiterate is that the diagnosis requires excluding invasive fungal disease, a problem which is expected to occur only in the context of immunodeficiency or advanced diabetes mellitus. Invasive fungal disease, when present, requires prolonged treatment with intravenous antifungal medications.

Treatment for AFRS involves steroids (both systemic and local), as well as treating bacterial co-infections as appropriate. In cases refractory to medical management, endoscopic sinus surgery is a reasonable next step, with a goal of removing allergic mucin and fungal debris as well as permanent drainage and ventilation of the sinuses [23]. Other treatments sometimes employed include allergy immunotherapy, systemic antifungals, and anti-IgE monoclonal antibodies. These options seem logical, but there is no clear evidence supporting their routine use.

Asthma

Asthma is a chronic disease characterized by bronchial hyperreactivity, airflow limitation, and respiratory symptoms [24] that improve with bronchodilator medications. Given that atopy is the strongest identifiable risk factor for this disease [24], it comes as little surprise that indoor molds have a role in its pathogenesis and symptomatology [15].

For patients with suspected or established asthma, investigation into potential allergic triggers (including molds) proceeds as discussed above. As ever, it is important to compare sensitization patterns found on allergy testing with clinical symptoms, with the understanding that sensitization does not equal allergy and many patients may be asymptomatically sensitized.

Mold proliferates in places that are humid and damp, whether indoors or outdoors. While so-called "outdoor" fungal allergens, typified by *Alternaria*, have traditionally been associated with severe asthma [25], a recent population based study showed that virtually all homes (99.9%) had detectable *Alternaria* on indoor environmental sampling [26], despite its traditional classification as an outdoor mold. Additionally, mold allergy is often accompanied by sensitization to other indoor allergens like dust mites and animal dander [14], which can also contribute to asthma, and the individual effects of mold may be difficult to disentangle from the relative contributions of these other allergens.

Another mold seen frequently (20–30%) in fungal asthma is *Aspergillus* [27]. This fact is noteworthy because IgE sensitization to *Aspergillus* is also a feature of Allergic Bronchopulmonary Aspergillosis (ABPA), which will be discussed in more detail below. The critical fact to remember here is that sensitization to *Aspergillus* is common in patients with allergic asthma, and the vast majority of these do not have ABPA.

Finally, with respect to the phenomenon of mold-triggered asthma, it may be useful to draw a distinction between primary and secondary effects of fungal exposure, as described in Portnoy et al. [3]. Primary effects involve the mold leading to the development of asthma, while secondary effects involve mold exposures exacerbating asthma that is already present. Multiple studies [3] suggest that molds play a role in both the development of asthma in the first place and exacerbations of preexisting asthma.

ABPA

Allergic Bronchopulmonary Aspergillosis (ABPA) is a condition resulting from hypersensitivity to *Aspergillus fumigatus* in the respiratory tract. Largely affecting patients with cystic fibrosis or asthma, the disease has an estimated prevalence of around 2% in patients with persistent asthma [28], and 2–15% in cystic fibrosis [28]. As with asthma itself, the pathophysiology involves the body's immune response skewing towards a T cell type 2 (Th2) pathway with characteristic IL-4, IL-5, and IL-13 release and accompanying IgE synthesis [9]. Left unchecked and untreated, the disease can ultimately lead to permanent damage to the lungs with bronchiectasis and fibrosis.

As suggested by the very name of the disease, the *Aspergillus* mold is predictably important in its pathogenesis and diagnosis. The spores of this ubiquitous mold, which is particularly associated with decaying vegetable matter [9], are inhaled by patients, and settle in the lower airways. In predisposed patients, the spores adhere to epithelial cells in the respiratory tract and cause cell damage via their proteolytic enzymes.

ABPA is often suspected in patients with cystic fibrosis or poorly-controlled asthma who have significant mucous plugging and unexpected pulmonary infiltrates on imaging [28]. These concerns are increased by the finding of IgE sensitization to *Aspergillus* on skin testing and serum testing.

For the diagnosis of ABPA in a patient with asthma, the following should be present [9, 28]:

1. Asthma
2. Immediate cutaneous reactivity to *Aspergillus*
3. Proximal bronchiectasis
4. Total IgE >417 kU/L or 1000 ng/mL
5. Elevated serum IgE and/or IgG to *Aspergillus* in comparison to skin test positive patients without ABPA diagnosis

Other features may also be present, including precipitating antibodies to *Aspergillus fumigatus*, current pulmonary infiltrates, and peripheral blood eosinophilia. A small number of patients may have concomitant AFRS.

The presence of sensitization to *Aspergillus* is necessary but not sufficient for diagnosis. As mentioned above, many patients, particularly with more severe phenotypes of allergic asthma, will be sensitized to *Aspergillus* but lack most of the other criteria. As the precise diagnosis informs treatment, the distinction is important.

Diagnosis of ABPA in the context of cystic fibrosis (CF) is similar to the above, except the presence of asthma is not obligatory. The Cystic Fibrosis Foundation Consensus Conference notes that pulmonary exacerbations in cystic fibrosis that do not respond to 1 week of antibiotics should prompt consideration of the diagnosis [29], and the same organization recommends yearly IgE screening in this vulnerable patient population. It is additionally worth noting that cystic fibrosis is historically a disease of childhood, and as such, CF-driven ABPA is seen in younger patients than asthmatic ABPA.

Treatment of ABPA is aimed at decreasing inflammation as well as organism burden [30]. The mainstay of treatment is oral glucocorticoids, often for several months and sometimes lifelong. Antifungal medications such as itraconazole and voriconazole also have an important role in treatment, with some providers prescribing them to all patients with acute symptomatic disease [30] and others reserving them for patients with acute exacerbations and/or difficulty coming off steroids. Poor prognostic factors include pulmonary fibrosis, extensive central bronchiectasis, and inability to taper off steroids.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a heterogeneous disease characterized by pulmonary inflammation which can lead to fibrosis [14]. It is caused by inhalation of a variety of environmental and occupational allergens on airborne organic particles [14].

HP can be acute, subacute, or chronic, though overlap between the stages is common. Acute disease involves influenza-like pulmonary and systemic symptoms in close association with antigen exposure, and resolves within hours to days of cessation of that exposure [31]. As the symptoms are fairly nonspecific and the precipitating antigen often not known, it is common for such a presentation to be mislabeled as a bacterial or viral syndrome. Histologically, the acute phase is characterized by a mononuclear cell pneumonitis [14]. If the exposure is ongoing, the patient enters a subacute phase with development of progressive dyspnea, fatigue, and cough over weeks to months [31]. Histologically, this phase is associated with interstitial granulomas [14]. The chronic stage involves dyspnea, weight loss, cough, and digital clubbing; histologically, interstitial fibrosis is seen [14, 31]. Patients in this stage often present with no discernable acute exacerbations; rather, they have a slowly insidious and progressive decline in lung function [31].

The most common allergens involved in HP are actinomycetes, fungi, and bird proteins; often, a mixture is required to cause symptoms [31]. The precipitating exposures tend to be occupationally-driven, as in farming, but fungal home

contamination is a factor as well [14]. This is particularly seen in cases of Japanese summer-type HP [32], linked to *Trichosporon* species which find favorable conditions for growth in damp traditional Japanese houses.

Other molds can trigger HP as well, but these cases are rarely seen outside of very specific occupational exposures. Many of these are described by single case reports in the HP literature, with allergen exposures at extremely high levels [14]. Sugar cane workers, for example, are at risk for Bagassosis precipitated by *T. vulgaris* species [31]. Mushroom workers are at risk for several rare subtypes of HP caused by *Penicillium* and *T. sacchari* [31] A host of other professions are potentially afflicted as well, including malt workers, maple bark strippers, woodworkers, paprika slicers, wine makers, and cheese washers [31]. These molds are unlikely to precipitate disease in patients without particular occupational exposures, and some experts maintain that fungal spores in isolation are actually uncommon factors in this diagnosis [14].

The mainstay of treatment is allergen avoidance. Sometimes this requires a complete break with the offending environment; other times, high-quality respirators and other occupational modifications are sufficient [31]. Patient and employer compliance can be an issue. Among pharmacologic treatments, systemic steroids are most frequently used. In the case of subacute disease, a relatively short course of 3–6 months is often sufficient if used in combination with allergen avoidance [31]. For chronic disease, longer courses of steroids are often necessary and some patients require lung transplant due to irreversible pulmonary fibrosis and development of pulmonary hypertension [31].

Toxic Mold Syndromes: Public Concerns and Current Scientific Knowledge

Up to this point, this article has focused on scientifically-accepted, plausible impacts of mold on health and human disease. However, molds have also been accused of having a variety of other effects via environmental mycotoxin exposure (as opposed to agricultural grain contamination), which have often been linked to an otherwise unexplained variety of symptoms that have concerned the general public searching for answers. Such concerns have led clinicians to seek further understanding in order to manage patient expectations. This line of pursuit for answers has also led to mitigation efforts, some not always well placed or effective, and has cost billions of dollars a year [14] both in mold removal/cleanup and in settled lawsuits.

Much of the historical basis for this public concern around possible toxic mold syndromes stems from a 1998 paper describing ten cases of acute pulmonary hemorrhage in infants in the Cleveland area [33]. The homes of these infants had significant water damage and indoor *Stachybotrys* species spore counts were elevated, suggesting a possible link. Around the same time, the CDC convened a working group of scientists to review this association [34]. The working group found

methodologic flaws in the original paper, including "statistically unstable and potentially inflated" odds ratios, nonblinded and aggressive collection of mold sample, and probable epidemiologic confounding by water damage [34]. The conclusion of the working group was that "on the basis of these limitations the evidence from these studies was not of sufficient quality to support an association between *S. chartarum* and AIPH [acute idiopathic pulmonary hemorrhage]" [34].

Since the publication of the 1998 paper, individuals looking for answers have fueled a movement around this idea of toxic mold and related "sick building syndrome." Proponents who sincerely believe in these disorders rely on otherwise seemingly unexplainable subjective sensory symptoms such as headache, fatigue, and difficulty concentrating, allegedly linked to fungal growth in indoor settings. However, the correlation between mold spore counts and these symptoms is weak at best [35, 36] and no evidence of association can be made with certainty. Experts estimate that for such symptoms to develop in adult patients, either short bursts of spores in excess of 10^6 per cubic meter or chronic exposures of >1000 toxin-containing spores per cubic meter would be required [36], which would be virtually impossible outside of rare agricultural settings. The amounts of "toxic mold" spores in the homes described in the 1998 paper on the topic, for example, were nearly undetectable at <10 per cubic meter [33, 36].

For all of these reasons, the American College of Occupational and Environmental Medicine reached the conclusion that "current scientific evidence does not support the proposition that human health has been adversely affected by inhaled mycotoxins in home, school, or office environments" [35]. Despite authoritative statements like the above, there continues to be a great deal of public concern regarding *Stachybotrys* and "toxic mold" in general.

For clinicians faced with helping to provide answers to these patients, diagnostic avenues that may help uncover the specific etiology of the patient's symptoms depend on the nature of the patient's presentation. If the clinical picture is consistent with allergic rhinitis or asthma, determination of mold, pollen, and/or animal dander IgE sensitivity can be performed and appropriate avoidance, remediation, and treatment measures can be implemented. If these disorders are thought less consistent with the patient's presentation, a reasonable next step would be to determine whether symptoms are consistent with any of the other known disorders associated with mold exposure such as HP and ABPA as outlined above. For the patients with vague or non-specific symptoms, the diagnostic process and determination of treatment options are sometimes more difficult. Educating the patients on the absence of any link between mold toxins and human health, outlined above, may be reassuring to some. Additionally, other diagnoses, depending on the presenting symptoms, should also be considered outside the context of mold exposure and should be evaluated appropriately. These may include disorders such as inducible laryngeal obstruction, chronic fatigue syndrome, and consideration of an untreated psychiatric comorbidity, as just a few examples.

Conclusion

Molds are ubiquitous in both indoor and outdoor environments. In the vast majority of cases, humans and molds co-exist without problems. In predisposed individuals, however, molds can lead to allergic rhinitis and complicate allergic asthma. Less frequently, fungi can lead to atopic conditions such as allergic bronchopulmonary aspergillosis and allergic fungal rhinosinusitis. Significant adverse health effects due to mycotoxins, rather than due to allergic sensitization, are unlikely outside of agricultural food exposures.

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Occupational Exposome and Lung Health

Maeve G. MacMurdo, Daniel A. Culver, and Mridu Gulati

Introduction

The average employed adult will spend between 60 and 90,000 hours at work throughout their lifetime [1]. Where and how you work impacts the exposome you inhabit, and has significant implications for respiratory health. Occupational lung disease remains a significant contributor to global respiratory morbidity and mortality. Patterns of globalization have altered the prevalence of occupational lung disease and shifted much of the burden of chronic occupational lung disease to the developing world. Meanwhile new technologies and production methods have resulted in new occupational lung diseases. Despite advances in technology, worker protections remain limited in many settings across both the developed and developing world.

Occupational safety and health directly impact respiratory health. Occupational exposures can result in a diverse range of respiratory conditions, from airways disease to interstitial lung diseases (Table 1). In this chapter, we will highlight a range of potential occupational lung diseases associated with specific industries focusing on non-infectious and non-malignant disease.

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Table 1 Examples of occupational lung disease by selected industries

Airways disease
Asthma (see Table 2)
Work related asthma
Irritant induced asthma
Sensitizer induced asthma
COPD
Smelter workers, machine operators, cleaners, coalminers, cotton workers, construction workers and bus drivers [23–25].
Interstitial lung and small airways disease
Pneumoconioses
Coal dust
Silica- (Benchtop fabricator, ceramics worker, miner, quarry worker, stonemason, sandblaster, tunneller)
Asbestos (Construction worker, electrician, mechanic, miner, railway worker, shipyard worker, carpenter)
Hypersensitivity pneumonitis
Bacteria (farmer, machinist, compost worker, swimming pool/spa);
Fungi (cheese worker, mushroom worker, tobacco grower, woodworker; animal proteins (birds, lab worker, textile worker)
Low molecular weight chemicals (polyurethane foam worker, painter)
Granulomatous lung disease
Chronic beryllium disease (aerospace machining and fabrication, nuclear industry, construction work, automotive fabricators)
World Trade Center Sarcoid-Like Granulomatous Disease
Cobalt (tool sharpeners, diamond polishers)
Aluminum (metal recycler, aircraft industry)
Obliterative bronchiolitis
Diacetyl induced (flavoring manufacturer, microwave popcorn manufacturers)
Constrictive bronchiolitis due to military deployment
Fiberglass reinforced plastics (boat builders)
Malignancy of the lungs
Lung cancer
Asbestos exposure, silica, radon, arsenic, PAH, diesel exhaust, cadmium, steel, nickel, chromium VI
Mesothelioma
Asbestos

Occupational Asthma

Occupational asthma is the most commonly diagnosed occupational lung disease globally and is generally underappreciated. An estimated 10–15% of adult asthma cases are related to occupational exposures, and approximately 20% of asthmatics report asthma symptom exacerbated by workplace exposures [2]. Occupational asthma can be sub-divided into three major categories- occupational asthma, work exacerbated asthma and acute reactive airway disease, also known as irritant induced asthma [2, 4].

Table 2 Occupational exposures and antigens associated with occupational asthma [2]

Sensitizer induced asthma	High molecular weight antigens	Cereals, flour, seafood proteins, animal antigens, detergent enzymes, latex, coffee beans
	Low molecular weight antigens	Isocyanates, red cedar dust, formaldehyde, persulfates, platinum, chromium, copper, acrylates, reactive dyes
Irritant induced asthma	Inhaled irritant	Cleaning agents, bleaching agents, acids, ammonia, sulfur dioxide, formaldehyde

Occupational asthma is characterized by a variety of respiratory symptoms including episodic cough, wheeze and dyspnea. The majority of occupational asthma develops as a result of exposure to an immune mediating sensitizer [2, 4–6]. The average latency between initial exposure to the sensitizing agent and development of clinical asthma is variable, but can occur as late as 10 years after first exposure to the agent [6].

Sensitizers can be categorized as high molecular weight (HMW) antigens (such as plant and animal antigens) or low molecular weight (LMW) antigens (such as wood-dusts and isocyanates) [2] (Table 2).

The majority of HMW antigens appear to induce asthma through an IgE mediated process. Patients with HMW antigen induced occupational asthma characteristically have detectable serum antibodies to the offending antigen, and describe acute onset of wheezing and dyspnea within minutes to hours of exposure [7]. By contrast, the process through which LMW antigens induce occupational asthma remains poorly understood. Some appear to act as a hapten — facilitating the binding of self-protein and generating airway inflammation. Others, particularly platinum and chromium, appear to induce asthma through an IgE mediated pathway [4, 7]. The asthma symptoms associated with LMW antigen occupational asthma are typically delayed, developing 4–8 h following initial exposure. Understanding the timing between exposure and symptom onset for these antigen groups is key to making a diagnosis of occupational asthma.

Globally, isocyanates remain one of the largest contributors to occupational asthma, with 1–30% of isocyanate exposed workers developing occupational asthma during employment [8, 9]. Isocyanates are widely utilized in automobile and aerospace manufacturing, as well as in commercial and residential remodeling. Car body shop mechanics and industrial painters are at particularly high risk due to use of polyurethane spray paints [10, 11]. While the risk of developing occupational asthma appears to be higher with higher concentrations and longer durations of exposure, isocyanate induced occupational asthma can occur at any level of exposure [2, 8].

In areas with significant forestry, exposure to western red cedar is also a major risk factor for the development of occupational asthma asthma [12, 13]. Cases of occupational asthma have also been reported among snow-crab, prawn and oyster processers [7, 14].

Irritant induced asthma is a non-immunologic form of asthma that follows exposure to irritants. First described in the 1980's, irritant induced asthma (also known as reactive airways syndrome) was classically characterized by the onset of asthma like symptoms within 24 h of exposure to an inhaled irritant [3]. A variant of this irritant induced asthma was seen among first responders following the World Trade Center disaster [15]. It is increasingly recognized the irritant induced asthma may present more gradually (within days to weeks of the initial exposure) [3]. Irritant induced asthma may also develop as a result of chronic lower level exposures to inhaled irritants, particularly cleaning products [16]. Exposure to bleach and ammonia based cleaning products has been associated with an increased risk of irritant induced asthma. Cleaners, who have persistent exposure to these chemicals are at high risk for irritant induced asthma syndromes [16].

Identifying occupational asthma early in the clinical course is key. A history of asthma symptoms that improve over the weekend or on vacation should prompt a high degree of clinical suspicion. In the early stages of disease, full recovery may be possible with removal from exposure. However, with prolonged ongoing exposure chronic pulmonary inflammation may develop, leading to persistent difficult to control asthma symptoms and significant asthma related morbidity [5, 13]. Due to the low level of antigen needed to trigger ongoing symptoms, removal from exposure typically requires removal from the workplace. Given this, the diagnosis should be made carefully and thoroughly. In contrast, triggers for patients with irritant induced asthma, unlike sensitizer induced asthma, are not specific to the causative agent.

As in all occupational respiratory diseases, history and a high index of clinical suspicion is the critical first step (Fig. 1). Temporal associations between exposures and respiratory symptoms are often uncovered, with many individuals reporting improvement away from work [2, 17] History and clinical judgment are sufficient to make the diagnosis. In the office setting, spirometry with evidence of a positive bronchodilator response can also support the diagnosis. Broncho-provocation testing can be considered, particularly to rule out the diagnosis in the setting of a negative test [2].

Unfortunately, asthmatics may demonstrate completely normal lung function away from exposure. Documenting the presence of airflow limitations at work can be quite informative. Serial workplace peak expiratory flow measurements are a useful alternative, and have relatively high sensitivity and specificity for occupational asthma [2, 18]. Ideally this testing should be performed for at least 4 weeks, with a period of time capturing data away from suspected exposure [2, 4]. Evidence of a clear difference in peak flows, or loss of diurnal peak flow variation are suggestive of an occupational trigger [2].

Industry Associated Occupational Lung Disease

The majority of patients will not present with a pre-specified diagnosis of occupational lung disease. Instead, identification of an underlying occupational lung disease is most commonly made through a thorough occupational history, and

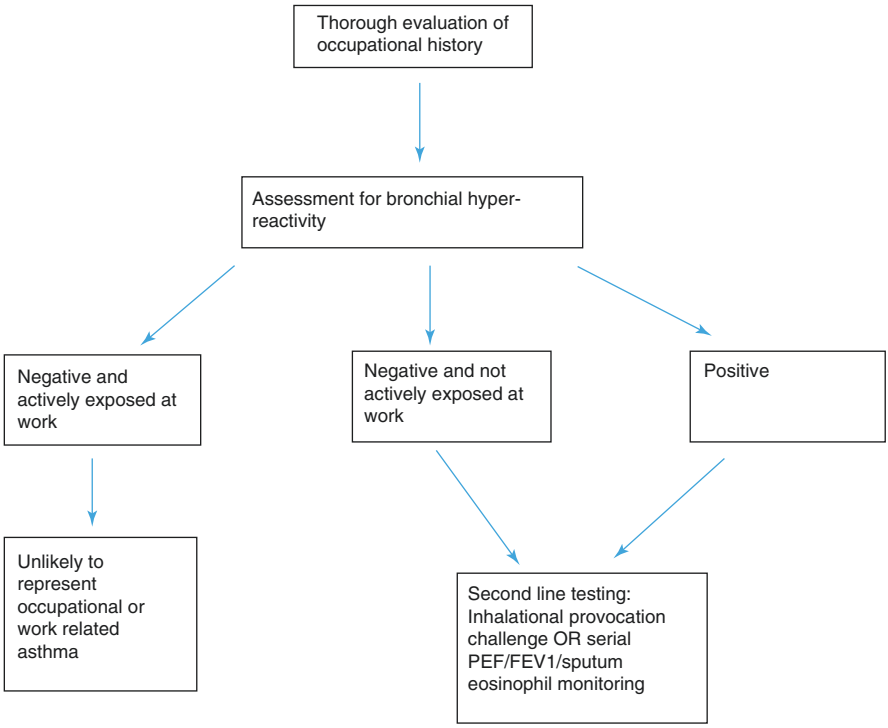

Fig. 1 Diagnostic pathway for evaluation of occupational/work related asthma [16]

identification of relevant occupational exposures. In the following sections, we will highlight occupational lung diseases associated with specific industries and provide a framework for evaluation of these conditions.

Agricultural Associated Respiratory Disease

"Farming" is a broad term for what can encompass a range of occupations and exposure patterns. The specific animals or crops farmed, the type of farm equipment utilized and the surrounding climate all impact risk of developing farming associated occupational lung disease.

That farming is not just an occupation, but a lifestyle cannot be under-emphasized. The majority of farmers will work and live in the agricultural environment-posing significant challenges in management where exposure limitation is necessary. Spouses of farmers, even when working off the farm, are exposed to many of the same risk factors as farmers themselves. Agriculture creates a unique exposome of exposure. The variety of potential antigens associated with agricultural work leads to a range of occupational lung diseases, due to both immune mediated and non-immune mediated processes.

Farmers Lung

Farmer's lung is a hypersensitivity pneumonitis syndrome, caused by an immune reaction to bacterial and fungal spores in damp hay and livestock feed. While a number of bacterial and fungal spores have been associated with the condition, sensitivity to aspergillus or Thermophilic actinomyces species is most commonly identified [19].

The prevalence of farmer's lung varies widely. In large cohort studies of agricultural workers, between 0.1% and 4.4% of farmers had clinical evidence of farmer's lung [19–22]. A further 5–20% of farm workers have detectable serum antibodies against aspergillus and Thermoactinomyces, suggesting risk for hypersensitivity development [20]. Conditions that promote microbial growth increase the risk of developing farmer's lung (FHP). Livestock farmers who are required to handle feed are at increased risk, as are those faming in damper northern climates [20, 22]. Conversely rapidly drying hay has been associated with decreased spore development [20, 22].

FHP is described as occurring in three phases- acute, subacute and chronic FHP. In clinical practice, distinguishing between sub-acute and chronic FHP may prove challenging. Even patients with chronic FHP may experience symptom "flares" which mimic acute HP, further confounding clear separation.

The acute phase of FHP is primarily driven by a type III hypersensitivity reaction. Exposure to large volumes of small inhaled antigens in a previously sensitized individual leads to activation of the pulmonary immune response, characterized by acute onset of dyspnea, fevers, cough, and malaise [23, 24]. Symptoms and imaging findings generally resolve with removal from exposure.

While acute FHP is commonly described in the literature, many patients experience a more sub-acute course, particularly in the setting of ongoing antigen exposure. Patients may report similar symptoms of dyspnea, cough and low grade fevers, occurring during work and resolving during weekends or with prolonged absence from the exposure. These chronic symptoms may be interspersed with occasional "flares" related to higher level antigen exposure. With prolonged exposure, chronic FHP develops. This is characterized by ongoing low level TH-2 lymphocyte activity and chronic inflammation, which progresses to widespread fibrosis.

Workup for FHP should begin with a clinical history. FHP should be considered in any worker exposed to hay, wheat or livestock who presents with acute or progressive dyspnea. Physical examination is frequently normal, though in some cases inspiratory crackles may be audible; inspiratory squeaks or "squawks" favor hypersensitivity pneumonitis over IPF. Spirometry may be variable, though restrictive defects are commonly seen [23–25]. Chest imaging findings vary depending on whether patients present with an acute or chronic phenotype. The CXR in acute FHP may mimic pulmonary edema, with HRCT confirming the presence of diffuse ground glass infiltrates and poorly defined centrilobular nodularity [23]. In patients with sub-acute or chronic FHP reticulation, honeycombing and traction bronchiectasis may be prominent on CT imaging, and can easily be mistaken for idiopathic

pulmonary fibrosis [23, 24]. Air trapping representing small airways disease may be noted, and can help to distinguish between the two conditions.

Specific IgG antibody testing or precipitins for a variety of putative antigens such as Aspergillus species, Micropolyspora faeni and Thermoactinomyces actinomyces may be performed. False negatives may occur due to time away from exposure or due to the fact that the particular assay does not specifically identified the causative antigen [25, 26]. False positives may simply reflect exposure, as studies have demonstrated high levels of positivity amongst asymptomatic farmers [27].

While in many cases an HP diagnosis may be made confidently on the basis of imaging and history, certain cases may require invasive sampling. Bronchoalveolar lavage can be performed, and is characterized by a strong lymphocyte predominance (typically greater than 20%) [28]. While commonly cited, a low lymphocyte CD4/CD8 ratio is neither sensitive nor specific, and routine use in diagnosis is not recommended [28]. Transbronchial biopsy can be performed. Classically biopsies will demonstrate lymphocytic interstitial pneumonia, peribronchiolar infiltrates and poorly formed granulomas [23]. Surgical lung biopsy may also be considered. For a full discussion of the histopathologic findings in HP, see Chap. 5.

Once diagnosed, the primary treatment for both acute and chronic FHP is antigen avoidance. Removal from exposure has been associated with an improvement in short term survival, and a decrease in the rate of DLCO decline. This benefit is less pronounced in those with fibrotic FHP [29]. However, especially in the context of farming, where antigen avoidance typically involves both a loss of income and a loss of housing full antigen avoidance may prove challenging, and create significant financial hardship.

In patients for whom those for whom antigen avoidance is not possible, or does not result in complete resolution of symptoms, a trial of corticosteroids should be considered. While dosing varies, a 4–8 week course of 40–60 mg of prednisone daily followed by a gradual taper is recommended, and has shown some evidence of improved FVC in patients without fibrotic lung disease [23, 25, 29]. In patients with chronic FHP, steroid sparing agents such as mycophenolate, leflunomide or azathioprine may slow disease progression and improve DLCO [30]. Recent evidence suggests that nintedanib may slow lung function decline in patients with progressive fibrotic HP [31]. For those patients who fail to respond to immunosuppressive therapy, referral for lung transplantation evaluation should be considered.

While farmer's lung remains the most common cause of HP in agricultural workers, outbreaks of hypersensitivity pneumonitis have been described among a number of other worker groups. For a description of high risk occupational exposures and their associated antigen, see Table 1.

Primary and secondary prevention should be recommended to farmers. Individuals should be encouraged to use PPE during handling of hay and feed though practically this may prove challenging. While full-face masks may be adequate in some cases, for those with severe FHP, self-contained pressure demand respirators may be required [20].

Drying wet hay and grain prior to storage is effective in reducing the risk of fungal spore exposure- however this may often be expensive and impractical. If

possible, hay with a high risk of spoilage should be stored in silage rather than in bales. Additionally, attention should be paid to ventilation in areas where large amounts of dusty material will be stored. Farm chores which involve handling hay or feed should be mechanized where able—though again this may prove cost prohibitive, especially for smaller farms. Finally, wetting down of dust prior to cleaning barns and stables may be effective as a measure to reduce aerosolization of fungal spores.

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) is an acute non-immune mediated syndrome triggered by exposure to high levels of organic dust. While typically not life-threatening, ODTS is extremely common among agricultural workers. Between 30% and 40% of workers exposed to agricultural organic dust will experience at least once episode of ODTS during their employment [32]. Workers in hoggeries are particularly at risk, with up to 70% of swine workers reporting at least one episode of work related respiratory distress [33]. Case clusters have also been reported among shrimp processing workers, and even in fraternities where large volumes of hay were utilized for decoration [32, 34, 35].

The presentation of ODTS is similar to that of acute hypersensitivity pneumonitis, with acute onset of dyspnea, fever, myalgias and cough 4–8 hours following organic dust exposure. While the clinical presentation is similar to HP, unlike acute HP, ODTS is not antibody mediated [20, 32]. Instead, inhalation of large volumes of bacterial endotoxin contained within these organic dusts triggers an acute inflammatory response [20, 32]. Imaging and physical examination are typically unremarkable, and symptoms will resolve within 24–48 hours of initial exposure [36].

To date, there is no evidence of long term pulmonary complications associated with ODTS [20, 33]. Given the acute nature of symptom onset and the fairly rapid resolution, it is likely that ODTS is significantly under-reported. Utilization of appropriate PPE when high levels of organic dust are anticipated effectively prevents ODTS, and should be recommended in all at risk workers [32].

Silo Fillers Disease

Silo fillers disease is a non-immune mediated complication of occupational exposure to nitrogen dioxide (NO_2) produced by silage (livestock feed produced by fermenting green forage) [37]. First reported in the early 1950s, silo fillers disease occurs across a spectrum of severity, ranging from mild dyspnea to death [38, 39].

Silage, the end product of fermenting a high moisture crop used for feeding livestock is stored in silos- large, vertical storage devices made of cement or steel.

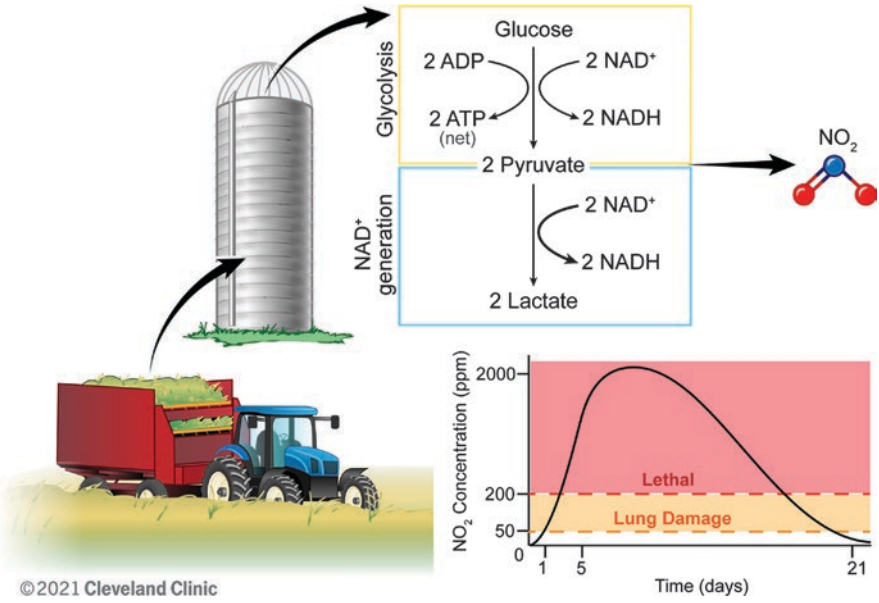

Fig. 2 Green materials are placed in the silo and undergo fermentation, resulting in the release of NO_2. Levels remain elevated in the 1–2 weeks post filling

Green materials such as oats, standing corn or alfalfa are placed within these silos and undergo fermentation [38]. Within a day of silo filling, concentrations of NO_2 rapidly reach toxic levels, often in excess of 200 ppm. Elevations in NO_2 persist for the first 1–2 weeks post-filling even in a well constructed silo, can remain elevated for as long as 6 weeks [38] (Fig. 2).

While the hazards of NO_2 are well known by most farmers, accidental exposure to elevated NO_2 remains relatively common [37]. Failure of unloading equipment or accidental loss of a tool in a freshly filled silo are the most commonly cited reasons for NO_2 exposure among cases [39]. Accidental exposure in temporary workers who are unaware of the potential for silo-fillers lung disease is also common [40, 41].

The severity of disease is determined by level and duration of exposure to NO_2 [38, 42–44]. Acute high level exposure to NO_2 is characterized by the immediate onset of dyspnea, wheeze and rapidly progressive encephalopathy. Loss of consciousness is common, leading to rapid death from asphyxiation in those who are not removed from exposure immediately [38, 42]. If exposure removal is achieved, initial pulmonary symptoms will rapidly resolve. Four to twelve hours post initial symptom resolution, rebound acute lung injury may develop. Characterized by profound hypoxic respiratory failure and diffuse bilateral pulmonary infiltrates, patients present in florid acute respiratory distress syndrome (ARDS) [38, 39, 44, 45]. Treatment of NO_2 associated ARDS with steroids is often initiated, though data are limited to case reports and animal studies [37, 38, 46]. In many cases, this secondary ARDS may prove fatal [37, 38, 46].

Prolonged, lower level exposure to NO_2 can result in a clinical picture more suggestive of bronchiolitis obliterans, with dyspnea, cough and diffuse bilateral nodular infiltrates [43]. Systemic symptoms may also be reported, including fever, chills and fatigue [43]. PFT testing in these patients may reveal evidence of obstructive physiology, with a decreased DLCO [38, 43]. Unlike the bronchiolitis obliterans reported with other occupational exposures, the majority of patients presenting with subacute silo fillers disease experience a gradual improvement in symptoms with removal from exposure. Cases of chronic bronchiolitis obliterans secondary to silo fillers disease have been reported, though they are relatively uncommon [38, 39].

Primary prevention of silo fillers lung focuses on training farmers to avoid entering upright or horizontal silos in the 2–3 week period following silo filling. If the silo must be entered during this time period, the silo should be ventilated for 30 min prior to entry, and a self-contained breathing apparatus should be utilized. Use of a buddy system during periods of silo entry should be strongly encouraged.

Manufacturing

Manufacturing evolves continuously. Some advances in technology have reduced the risk of occupational lung disease. Others have resulted in new exposures, and new clinical syndromes. With globalization, a significant burden of occupational lung disease related to manufacturing has been shifted to the developing world. The risk of occupational lung disease secondary to manufacturing is determined not only by the type of manufacturing, but by job specific exposures. Careful assessment of both duration and intensity of exposure is key in determining risk of disease.

Lung Disease Associated with Food Manufacturing

Flavoring Associated Bronchiolitis Obliterans

Diacetyl is utilized widely in food processing, giving foods an artificial butter flavor. While considered generally safe for human consumption, inhalation of diacetyl is associated with the development of severe bronchiolitis obliterans.

Pulmonary disease associated with diacetyl inhalation was first described in animal studies in the early 1990s [47, 48]. In 2000, “popcorn workers’ lung” was reported after a series of workers in a microwave popcorn production facility were found to have profound fixed obstructive ventilator defects due to bronchiolitis obliterans (BO) [47, 48]. Since these initial cases, additional clusters of diacetyl

induced lung disease have been reported among artificial flavor workers, including coffee bean roasters and cookie dough manufacturers. Additionally, a flavoring substitute for diacetyl, 2,3-pentanedione, has also been associated with BO. Workers directly involved in mixing flavorings are at highest risk, though in factories without adequate ventilator controls, all workers have the potential for exposure [47, 49, 50].

BO is a disease of the small airways, and presents initially with non-specific respiratory symptoms, including dyspnea, cough and reduced exercise tolerance [50, 51]. Timing from exposure to onset of disease is relatively rapid, with an average latency of 1.5 years [48, 52]. Patients with BO generally experience no improvement in symptoms with removal from exposure [47, 51].

Pulmonary function testing in the early stages of BO may be relatively unremarkable. As disease progresses, a profound ongoing decrease in FEV1 is noted, with the development of a fixed obstructive deficit over time [51]. A positive bronchodilator response may be seen in some patients, and misdiagnosis as asthma or emphysema is common in this patient population. Restrictive defects in PFTS have also been described in exposed workers, though are less common [50].

HRCT should be obtained in all patients with a concern for BO, and should include expiratory phase imaging to allow detection of air trapping and mosaic attenuation [51] In cases with a clear occupational history and PFTS suggestive of BO, biopsy is not recommended [50, 51]. Surgical lung biopsy may be performed in cases where the diagnosis is in question, though the potential for false negative biopsies is relatively high due to significant geographic and temporal heterogeneity of bronchiolar disease [51].

No treatment for BO exists with the exception of lung transplant. Trials of immunosuppression have been largely ineffective. Use of inhaled steroids and azithromycin have been described, it is recommended to discontinue these therapies if patients do not report significant benefit after a brief trial [51, 53].

In response to the growing body of evidence that diacetyl inhalation was associated with BO limits on allowable respirable diacetyl have been recommended by the National Institute for Occupational Health and Safety (NIOSH) [54]. Restrictions on respirable diacetyl outside of the US remain limited [49, 50, 52, 55, 56].

All workers with occupational exposure to diacetyl or other artificial butter flavorings are now recommended to undergo six monthly spirometry screening. A 15% fall in FEV1 over 12 months should raise concern for the development of BO and prompt formal assessment and possible reassignment, even if FEV1 remains within a “normal” range [50]. Removal from exposure prevents further decline in FEV1, but does not result in recovery of previous lung function.

While substitution or elimination of diacetyl containing products is the most effective mechanism for preventing BO, the potential pulmonary risk of exposure to substitute products is not yet known. Given that, engineering controls which ensure adequate ventilation and reduce worker exposure are recommended.

Lung Disease Associated with Textile Manufacturing

Byssinosis

Byssinosis is a occupational airway disease caused by inhalation of raw flax, hemp and cotton dust. In the US, cotton dust is the most common cause of byssinosis; it has been proposed that endotoxin from gram negative rods in the cotton dust contributes to disease pathogenesis [56].

Rates of byssinosis across the US and UK were significantly reduced with the introduction of a occupational standard for allowable respiratory cotton dust and enforcement of strict workplace controls [57]. Production of cotton has now shifted to the developing world, where byssinosis remains a significant health concern [58].

Acute byssinosis is characterized by acute onset of dyspnea, cough and wheezing following exposure to cotton dust [59, 60]. Also known as "Monday asthma" or "Monday Fever", acute byssinosis is typically most severe on the first day of return to work after the weekend due to transient removal from exposure. Acute byssinosis can be severe, resulting in high workforce turnover [59]. In workers with ongoing exposure, symptoms begin to occur consistently throughout the week. Over time, symptoms of dyspnea and cough persist even with removal of exposure—reflecting progression to chronic byssinosis [59].

The diagnosis of byssinosis is made on the basis of an occupational history and spirometric assessment, which reveals the presence of a fixed obstructive defect [60–62]. FEV1 continues to decline with ongoing exposure, and a serial decrease in FEV1 during workplace surveillance testing should prompt concern for the disorder. Imaging is variable, and classically mimics COPD.

Treatment of byssinosis should focus on exposure removal to prevent further decline. Patients with ongoing symptoms may benefit from inhaled therapies, similar to those utilized in chronic asthma.

Prevention of byssinosis is primarily focused on dust control- both through ensuring adequate ventilation through engineering controls in high dust exposure areas, providing appropriate PPE during high dust exposure activities, and utilizing washed cotton to reduce dust release [57].

Nylon Flock Workers Lung

Nylon Flock Workers Lung is an interstitial lung disease caused by exposure to flocking—a process in which nylon cut to an extremely fine level to create a velvet texture. Originally, it was believed that the nylon particles created by the flocking process were too large to be respirable. However, changes in the process of flocking production to increase efficiency and decrease cost resulted in the move towards the use of rotary cutting devices [63]. Unlike traditional guillotine cutting devices, these can easily become blunted- resulting in the release of smaller, respirable nylon particles.

Respiratory symptoms in flocking workers were first noted in Ontario in the 1990s after a cluster of workers within a single factory developed severe dyspnea, hypoxia and diffuse pulmonary infiltrates [64]. Initially symptoms were attributed to an unidentified fungal exposure. Reports of similar cases in nylon flockers across Rhode Island and Massachusetts, triggered a formal investigation by NIOSH [65, 66]. The use of rotary cutters leading to high levels of respirable nylon particles was identified in all factories.

Nylon Flock Workers' Lung Disease is characterized by the development of progressive dyspnea and cough following exposure to nylon flocking [66]. Symptoms are persistent, and continue even after removal from initial exposure. PFT patterns within patient cohorts are variable, with the majority showing evidence of a restrictive process. Overlying reversible airway obstruction has also been reported [66]. Imaging is characterized by ground glass opacities in a peripheral distribution, with or without associated fibrosis [67].

Biopsy in Nylon Flock Workers' Lung disease classically shows a pattern of lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia [68]. However, significant variation on biopsy has been reported, leading some experts to suggest that rather than a strict pathologic criteria, a diagnosis should be made on the basis of respiratory symptoms, a clear occupational exposure, and pathology suggestive of ILD which is not clearly explained by an alternate cause [63, 69].

The majority of patients will recover with removal from exposure, though the process of recovery is slow [63]. Return of symptoms with return of exposure has been reported. Even with removal from exposure, some patients will continue to experience symptom progression and PFT decline [63]. Steroid treatment has been attempted in this population but has proved largely ineffective [63–65].

Mining and Heavy Industry

The lung disease associated with mining represents some of the oldest documented occupational respiratory conditions. The pneumoconioses are a group of interstitial lung diseases caused by inhalation of dust. While a number of exposures can result in the development of pneumoconiosis, asbestos, silica, and coal dust are among the most commonly reported.

Occupational lung disease associated with mining and heavy industry continues to cause significant morbidity and mortality, in both the developed and developing world. For example, over the past decade, rates of coal and silica associated lung disease have risen dramatically, reflecting changes in mining technique, and new occupational exposures [70–72]. In addition to the risk of pneumoconiosis development, exposures in these industries have been associated with chronic lung diseases such as COPD, diffuse dust fibrosis and lung cancer. Availability of screening, and options for treatment for workers diagnosed with mining related lung disease remain pressing issues.

Coal Dust Associated Lung Disease

Inhalational exposure to coal dust is associated with a spectrum of diseases, ranging from coal workers pneumoconiosis, COPD and dust related diffuse fibrosis. Patients with pneumoconiosis can present with either simple coal workers pneumoconiosis or complicated coal workers pneumoconiosis, also known as progressive massive fibrosis. (Table 3).

Coal mine dust contains a mix of carbon, crystalline silica and other trace minerals. Inhalation results in deposition in the terminal bronchioles, where it is engulfed by alveolar macrophages, resulting in the formation of localized nodules, and the release of pro-inflammatory cytokines, leading to scarring and fibrosis (Fig. 3) [70]. Coal rank- a quality of the coal seam which ranges from low rank, sub-bituminous coal, to higher ranking anthracitic coal, determines the relative concentrations of carbon, crystalline silica and trace minerals within coal dust [71]. Mining of higher ranked, anthracitic coal has been associated with a higher risk of pneumoconiosis in historical analyses, though the relevance of rank for risk of CWP is controversial.

The diagnosis of coal workers pneumoconiosis (CWP) is made on the basis of imaging findings, and is guided by the international labor office (ILO) classification throughout most of the world, with the exception of China, which uses the Chinese Roentgenodiagnostic Criteria of Pneumoconioses system [72, 73]. Imaging is classified according to the presence or absence of nodularity, nodule size, and nodule distribution.

Simple CWP is characterized by small (<1 cm) nodular opacities on chest x-ray. While classically these nodules have been described as having an upper lobe predominance, more recent research suggests that a large percentage of patients with simple CWP may have significant lower lobar nodularity [74]. Patients with simple CWP may be symptom free, or may report dyspnea, productive cough and wheeze. Again, while classic teaching states that pulmonary function testing is normal in patients with simple CWP, evidence globally suggests that even simple CWP may be associated with persistent PFT abnormalities [75, 76]. Abnormally low FEV1

Table 3 Spectrum of coal dust associated lung disease

	Imaging	Symptoms	Latency
Simple coal workers pneumoconiosis	<1 cm nodules	Asymptomatic, rare dyspnea, decreased exercise tolerance	5–15 years
Complicated coal workers pneumoconiosis	>1 cm nodules, irregular. Localized emphysema, fibrosis.	Dyspnea, cough, decreased exercise tolerance	5–15 years
Diffuse dust related fibrosis	Reticulation, traction bronchiectasis? Honeycombing	Slowly progressive dyspnea, cough, fatigue	10–20 years

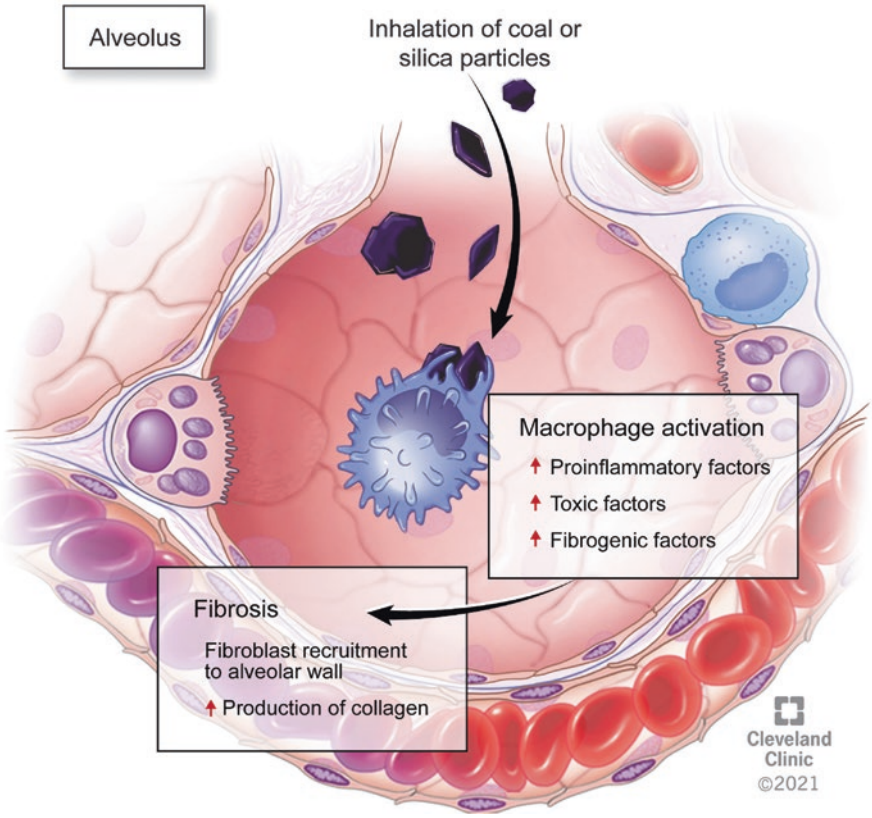

Fig. 3 Inhaled coal particles are deposited in the alveoli, resulting in macrophage activation and release of pro-inflammatory cytokines

measurements are common, and appear to correlate with increasing nodular proliferation [75, 76].

By comparison, complicated coal workers pneumoconiosis is characterized by coalescence of small pulmonary nodules into large (>1 cm), irregular nodules. While upper lobe distribution is typically described, nodularity can be seen throughout the lung fields, and may be accompanied by evidence of localized emphysema and fibrotic change. Patients are often significantly symptomatic, and may have substantial abnormalities in FEV1 and FVC, with evidence of focal obstruction or air trapping [77].

Also referred to as progressive massive fibrosis (PMF), rates of complicated CWP across the Unites States have steadily increased over the past decade. New diagnoses of complicated CWP among active miners have climbed to rates prior to the passage of the Federal Mine Health and Safety Act (FMHSA) in 1977 [74]. Reasons underlying this rapid rise in cases are likely multifactorial, including an

increase in slope mining, a move towards increased mining of high rank coal, a transition to thin seam mining and decreased compliance with FMHSA regulations [70].

The diagnosis of both simple and complicated CWP can be made on the basis of clinical presentation. Key features of the occupational history in the assessment of a patient with possible CWP include duration of mine work (typically CWP is seen after at least 10 years of exposure, though may occur earlier in the work course, particularly with higher levels of exposure), the type of mining performed (surface versus underground), job title and job duties. Particular jobs within mining are associated with higher volumes of inhaled dust exposure, particularly bolting and roof blasting.

In cases where the diagnosis is unclear, or atypical features are present, high resolution CT chest may be considered. HRCT is more sensitive for the detection of smaller nodules and air-trapping which may not be evident on CXR. In patients with consistent history and imaging, biopsy is rarely indicated.

While simple and complicated CWP are perhaps the most commonly recognized forms of coal dust associated lung disease, diffuse dust related fibrosis (DDF) is commonly reported on autopsy studies of miners [79]. Characterized by irregular consolidation, traction bronchiectasis and evidence of reticulation, DDF may be incorrectly diagnosed as interstitial pulmonary fibrosis (IPF) without a full occupational history. Patients with DDF have evidence of restrictive changes on PFTS, with reduced DLCO [79]. Biopsy if performed is significant for bridging fibrosis with interlobar septal pigmentation [78]. Nodular changes suggestive of CWP or silica exposure may be noted [78]. Compared with patients with IPF, patients with DDF appear to have a younger age of onset and somewhat more indolent course [78].

In addition to the spectrum of coal dust associated interstitial lung disease, inhalation of coal dust has been shown to result in chronic emphysematous changes and obstructive lung disease. Chronological studies of miners overtime shown that roughly 1 year of coal dust exposure is associated with a similar decline in FEV1 seen with 1 year of tobacco use [79, 80]. 35% of active coal miners report symptoms of chronic bronchitis, including productive cough, dyspnea and wheeze [81].

Limited treatment options exist for the spectrum of coal dust related lung disease. Further exposure should be limited if possible, though practically speaking this may prove challenging given the lack of alternative employment options in areas where coal mining is common. Lung transplant is indicated for those with severe, symptomatic disease, though rates of transplant for CWP remain relatively low.

The major mechanism of prevention for CWP is a reduction in exposure to respirable coal dust. In 2014, the Mine Health and Safety Administration released an updated final ruling on allowable respirable coal dust exposure, increasing the requirements for dust exposure monitoring, and reducing allowable dust concentrations to 1.5 mg/m [3] for underground and surface coal mines [82].

Silicosis

Silicosis is caused by exposure to crystalline silica. It can present as acute silicosis, chronic silicosis, or as accelerated chronic silicosis. First described among miners by Hippocrates, silicosis remains one of the most common causes of occupational lung disease on a global scale [83].

While mine workers are commonly perceived as being at highest risk for silicosis, exposure to silica is widespread in industries beyond mining. Workers are often unaware of their exposure to silica, and screening in these groups may be limited. A recent outbreak of silicosis among engineered stone fabricators across Australia, Belgium, Israel and the United States has highlighted the under-recognition of silica exposure in non-traditional industries [84–89]. Similarly, outbreaks of silicosis among diamond polishers across China and India highlight that across many industries, worker protections remain sub-optimal [90].

Silica exists in two forms. Amorphous silica is relatively inert, and is used widely in industry as a filler and anti-caking agent [91]. Crystalline silica, most commonly found in quartz, is responsible for the majority of respiratory complications associated with silica exposure [86]. Silica is present in various concentrations across many of the major rock types, ranging from granite and slate (which contain roughly 40% silica), to sandstone, which is comprised almost entirely of silica. Engineered stone, also known as Caesarstone or Silestone, is a mixture of composite quartz, and similar to sandstone, has an extremely high silica content.

When inhaled, crystalline silica lodges in the terminal bronchioles, where it is engulfed by respiratory macrophages. These respiratory macrophages trigger the release of IL-1 and TNF, initiating an inflammatory cascade [92, 93]. Over time, persistent inflammatory cytokine release results in the recruitment of type 2 pneumocytes and progression from inflammation to fibrosis [92].

Silicosis exists along a spectrum of disease severity that is primarily dictated by the degree and duration of exposure.

Acute silicoproteinosis develops in response to very high-level exposures to respirable crystalline silica. Now relatively rare, before the advent of respirable silica standards acute silicoproteinosis was a major driver of morbidity and mortality. Most infamously uncontrolled blasting of quartz containing rock in the construction of the Hawk's Nest Tunnel in West Virginia resulted in the deaths of between 500 and 1000 workers due to acute silicoproteinosis [94, 95].

The disease is characterized by the development of severe hypoxic respiratory failure in the days to weeks following exposure, with HRCT imaging characterized by lower lobe predominant infiltrates, ground glass opacities and centrilobar nodules [96, 97]. No treatment for acute silicoproteinosis exists, and mortality is high.

Simple silicosis is the most common form of the disease, and is characterized by the presence of small (<1 cm) silicotic nodules distributed throughout the lung fields, primarily in the upper lobes [98]. Simple silicosis typically develops after decades of exposure, and is frequently detected incidentally. In surveillance literature, between 30% and 50% of workers in high risk professions have evidence of

silicosis on initial screening [99–101]. Simple silicosis may not have a benign presentation. Workers may report cough, dyspnea and decreased exercise tolerance [102]. With increased burden of nodularity, evidence of obstructive or restrictive PFT changes may be noted [103].

Between 5% and 40% of workers with simple silicosis will progress to develop "complicated" silicosis, also known as progressive massive fibrosis (PMF) [86, 104]. This is characterized by coalescence of smaller silicotic nodules into large lesions greater than 2 cm in diameter, often with associated cavitation and significant fibrosis [102]. Patients with PMF are more likely to have significant respiratory symptom burden, and profound restriction, obstruction or mixed deficits on pulmonary function testing [86].

Rates of progression from simple to complicated silicosis vary, and are influenced by duration of exposure, frequency of high level exposures, exposure to tobacco products and host genetic factors [100, 105, 106].

Accelerated silicosis is characterized by a comparatively rapid progression from simple silicosis to PMF. Outbreaks of accelerated silicosis have been described in a number of worker groups, and are through to be due to more frequent exposure to high levels of respirable silica [87, 90]. Compared with traditional silicosis, patients with accelerated silicosis have rapid progression to significant disease burden, and are at increased risk of silica associated morbidity and mortality [85, 86, 90, 107].

In addition to the risk of developing silicosis, exposure to silica is associated with a number of other complications. Even when controlling for tobacco use, rates of COPD are higher in silica exposed workers [102]. Silica exposure, even in the absence of silicosis, is also associated with an increased risk of developing tuberculosis [109, 110]. This is thought to be related to suppression of the pulmonary immune system by inhaled silica. Particularly in countries where tuberculosis is endemic, the combined risk of tuberculosis and silicosis is of significant concern. Workers exposed to silica also have an increased risk of developing autoimmune diseases such as rheumatoid arthritis and may also develop chronic renal disease [108].

CXR has traditionally been used for silicosis screening, HRCT is more sensitive and specific for silicosis, particularly in the early stages of disease [109]. Classically, imaging in patients with silicosis is characterized by hilar lymphadenopathy with eggshell calcification, and diffuse nodules less than 1 cm in diameter. Pleural thickening is common, as is evidence of early fibrosis and distortion of the lung parenchyma [100, 106, 109].

In patients with a clear occupational history and classic imaging findings invasive testing is not necessary to confirm the diagnosis of silicosis. Bronchoalveolar lavage is typically non-diagnostic- the presence of silica in BAL fluid does not confirm the diagnosis of silicosis and may be seen in any silica exposed worker [98]. Biopsy may reveal silicotic nodules- characterized by concentric rings of fibrosis, resulting in an "onion skin" appearance [92].

With the exception of lung transplantation there is no treatment for silicosis. Even with removal from exposure, some workers will develop radiologic and symptomatic progression [99, 100]. Whole lung lavage has been attempted in a subgroup

of patients with acute and accelerated silicosis, but the usefulness of this is uncertain [110]. Prevention of silicosis is far more effective. Dust control measures, wet processing and personal protective equipment have all been shown to reduce respirable silica, and consequently the risk of silicosis.

Asbestosis

Asbestos exposure is associated with a range of pulmonary diseases, ranging in severity from benign pleural changes to rapidly progressive malignancy (Table 4). Utilization of asbestos in construction and manufacturing became widespread during the twenty-first century [111, 112]. A growing understanding of the harms associated with asbestos lead to widespread bans across the developed world. Despite this an estimated 125 million workers remain exposed to asbestos annually [112, 113]. Even in countries where use of asbestos is banned, demolition and remodeling of structures built with asbestosis results in an ongoing risk of exposure to workers.

Asbestos exists in two forms. Amphibole asbestos (which can be further subdivided into crocodolite, tremolite and amosite) is made up of straight, needle like fibers. In contrast, serpentine (christolyle) asbestosis consists of curved bundles of fibers. When these fibers are inhaled they become lodged in the terminal bronchioles, and are subsequently engulfed by alveolar macrophages [113, 114]. Macrophage phagocytosis of the asbestos fibers leads to macrophage death, triggering the release of reactive oxygen species, and initiating an inflammatory cascade [114]. These engulfed asbestos fibers are then either broken down, or remain in the terminal bronchiole, where they become covered in a layer of mucopolysaccharide and iron, forming asbestos bodies [113].

Table 4 Spectrum of asbestos related pulmonary disease

	Imaging	Symptoms	Latency
Pleural plaques	Sharply demarcated, asymmetric lesions on pleural surface	Minimal	10–20 years
Benign asbestos pleural effusion	Unilateral small to moderate effusion. Costophrenic angle blunting	Minimal	10–20 years
Diffuse pleural thickening	Ill-defined/irregular pleural thickening. Costophrenic angle blunting	None to mild dyspnea, exercise intolerance	10–20 years
Asbestosis	Lower lobe predominant band like opacification, septal thickening, pleural thickening	Progressive dyspnea, cough and decreased exercise tolerance	5–40 years
Malignant mesothelioma	Irregular pleural thickening, pleural effusion, interlobar fissural thickening	Progressive dyspnea, chest wall discomfort, chest pain	10–20 years

Benign pleural plaques are the most common symptom of occupational exposure to asbestos- these present as sharply demarcated, raised, asymmetric lesions on the bilateral pleural surfaces [115]. Typically asymptomatic, the majority of pleural plaques are found incidentally. Between 20% and 60% of workers exposed to asbestos will develop pleural plaques with a latency of 10–20 years from initial exposure [113]. Histologically pleural plaques are characterized by bland bundles of collagen fibers in a basket weave pattern [115]. While symptoms associated with pleural plaques are rare, longitudinal studies suggest that the presence of pleural plaques is associated with a small but significant decrease in FVC [116].

Diffuse pleural thickening may also been seen in workers with a history of asbestos exposure. This is characterized by ill-defined and irregular thickening of the pleura, with blunting of the costophrenic angle evident on CXR [117]. The risk of developing diffuse pleural thickening is increased with longer durations of asbestos exposure [118]. The presence of diffuse pleural thickening is associated with a decrease in FEV1 and FVC, though the functional limitation associated with this is typically low [116].

Asbestosis — fibrosis of the lungs secondary to asbestos exposure, was first described among asbestos miners in ancient Greece [119]. The risk of developing asbestosis appears to be related to duration and level of exposure. While the average latency from exposure to disease development is 20–40 years, cases of asbestosis have been described in workers who experience rapid high level exposures after as little as 5–10 years [120, 121]. Classically, patients will endorse insidious onset of dyspnea, cough, progressive decline in exercise tolerance and fatigue. Following symptom onset, a fairly rapid decline in FEV1 and FVC is seen with development of significant restrictive physiology [116].

On CXR, asbestosis is characterized by irregular bilateral lower lobe opacification, usually accompanied by other evidence of asbestos exposure such as pleural plaques or pleural thickening [115]. Similar to the other occupational pneumoconiosis, the ILO score is used to describe severity of imaging findings. High resolution CT chest is significantly more sensitive for asbestosis, and is characterized lower lobe predominant band-like opacifications, honeycombing, septal thickening and evidence of pleural plaques/pleural thickening [115, 122].

Three major criteria are required to confirm a diagnosis of asbestosis- imaging or histology consistent with the diagnosis, evidence of prior asbestos exposure (either through occupational history, evidence of other asbestos related imaging findings, or the presence of asbestos bodies within a sample), and lack of another more likely diagnosis [118, 119]. Of note, biopsy is not required to confirm the diagnosis of asbestosis and with imaging findings suggestive of disease, a clear occupational exposure is sufficient [119]. No treatment exists for asbestosis, with the exception of lung transplantation.

In addition to the pulmonary and pleural disease related to asbestos exposure, the risk of malignancy is also significantly increased. A large population study on insulation workers revealed that asbestos exposure was associated with a 6.8 fold increase in the risk of death from lung cancer- similar findings have been reported among other worker groups exposed to asbestos [123–125].

Along with an increased risk of primary lung cancer, risk of pleural malignancy, specifically malignant pleural mesothelioma is significantly increased in workers exposed to asbestos [120, 126]. The risk of mesothelioma appears to be increased with even with comparatively low level asbestos exposure, with documented cases among spouses of asbestos exposed workers and clerical staff [114, 124, 126]. The latency period between exposure to asbestos and development of malignancy remains prolonged, and rates of malignant mesothelioma among workers previously exposed to asbestos are anticipated to peak between 2010 and 2020, reflecting changes to occupational safety standards made decades earlier [127].

Malignant mesothelioma may remain minimally symptomatic until significant disease has developed. Dyspnea secondary to the development of pleural effusion is common, as is chest pain and chest wall pain due to tumor infiltration [128]. The diagnosis of malignant mesothelioma can prove challenging. Imaging changes are characterized by irregular pleural thickening, peripheral parenchymal lesions, pleural effusion and interlobar fissural thickening, however sensitivity in early disease may be poor [128, 129]. Pleural fluid cytology has roughly a 30% sensitivity for the diagnosis of malignant mesothelioma, and pleural biopsy is recommended if the diagnosis is in question [128, 130].

The prognosis for malignant mesothelioma is bleak, with an average survival of 8–12 months. Chemotherapy has been shown to prolong survival in some patients with malignant mesothelioma [128, 131]. Radiation may be considered as a palliative measure [128, 131].

Chronic Beryllium Disease

Chronic beryllium disease (CBD), or berylliosis a chronic granulomatous disease often indistinguishable from sarcoidosis that predominantly affects the lungs. Beryllium is widely utilized across industries ranging from aerospace and weapons manufacture to dentistry due to its unique chemical properties. Similar to hard metal, beryllium is light, exceptionally strong, and highly heat resistant. It is also associated with significant respiratory disease.

In susceptible workers, exposure to beryllium results in the development of beryllium sensitization, characterized by activation of beryllium specific CD4+ T cells [132–134]. Workers who develop beryllium sensitization are at risk of progression to (CBD), an interstitial lung disease characterized by diffuse granulomatous inflammation, similar to that seen with sarcoidosis. The risk of developing beryllium sensitization and subsequent CBD appears to be multifactorial, related both to job specific exposure and underlying genetic factors. Machinists (those who directly cut and shape beryllium) appear to be at highest risk of sensitization, possibly due to higher task related exposures. Variation in the HLA-DPB1 E69 allele appears to be a significant contributor to the risk of developing beryllium sensitivity. The presence of any DPB1 E69 allele is associated with a significantly increased risk of developing beryllium sensitization, and of progressing to CBD [135–139].

The majority of beryllium sensitization is detected through workplace screening utilizing the blood beryllium lymphocyte proliferation test (BeLPT), which is required as part of routine medical surveillance in beryllium exposed workers [140]. Occasionally, workers may present with CBD prior to a diagnosis of beryllium sensitization, though this is relatively uncommon. CBD is characterized by dyspnea, exercise limitation, weight loss and cough, similar to the symptoms seem with pulmonary sarcoidosis [45, 143]. Unlike sarcoidosis, extra-pulmonary manifestations are uncommon [140].

Pulmonary function testing may be normal at the time of initial diagnosis, though over time the majority of patients will develop obstructive, restrictive or mixed defects [141]. Impaired gas exchange during cardiopulmonary exercise testing is one of the earliest clinical indications of chronic beryllium disease, and may be seen prior to the onset of clinical symptoms [142].

For a worker to receive a diagnosis of beryllium sensitization they must have either two positive BeLPTS, a positive BeLPT followed by a "borderline" "BeLPT" or three "borderline" BeLPTS. In workers for whom suspicion of beryllium sensitization is high, BAL BeLPT is more sensitive and specific. A single positive BAL BeLPT is sufficient to confirm beryllium sensitization.

For a beryllium sensitized worker in whom the diagnosis of CBD is suspected, transbronchial biopsy is recommended. The presence of non-necrotizing granulomatous inflammation confirms the diagnosis. Imaging showing diffuse granulomatous lung disease can also support a diagnosis of CBD, though is usually not sufficient to obtain workers compensation. Particularly in the early stages of disease, imaging findings may be highly variable.

Not all patients with CBD will experience significant disease progression, though the vast majority will experience decline in pulmonary function over time [143–145]. This pattern of decline varies widely, ranging from steady deterioration to periods of stability interspersed with rapid decline. The decision to initiate treatment for CBD is based on the rate and pattern of this decline and or presence of severe debilitating symptoms [146]. Data to support treatment is limited, however steroid therapy is conventionally used as first line therapy [147]. Prednisone is typically started at a dose of 20–40 mg, then slowly tapered, similar to initial treatment of sarcoidosis [147]. The majority of patients will experience short term improvement with steroid therapy, though long term response is more variable. Steroid sparing agents should be considered in patients with progressive disease, or those requiring high dose corticosteroid therapy [146–148].

Increased duration of beryllium exposure is associated with an increased risk of CBD, and avoidance of further exposure on diagnosis of CBD is highly recommended. However, CBD develops in response to an altered pattern of autoimmunity, triggered by beryllium exposure. Given this it is likely that many patients will experience progression, even if they have no further direct exposure.

Primary prevention of CBD focuses on reducing exposure to beryllium, through engineering controls and appropriate personal protective equipment. A recent update to the OSHA standard for allowable beryllium exposure reduced the permissible exposure limit for beryllium to 0.2 $\mu g/m^3$ over an 8 h period [149]. It is

recognized that even a small amount of beryllium exposure can trigger disease. Regular medical surveillance can detect beryllium sensitization, and facilitate early exposure removal.

Hard Metal Lung Disease

Hard metal induced lung disease, also known as 'Cobalt Lung', or "Giant Cell Pneumonitis" is a spectrum of interstitial lung disease which develops secondary to exposure to hard metal- alloys of cobalt and tungsten fused together through a process known as cementation or sinestration [150–152]. Hard metal alloys, also referred to as cemented carbides, are extremely strong and heat resistant and are used widely throughout industry for cutting, polishing and machining [153].

The syndrome of Hard Metal Lung Disease (HMLD) was first described in the early 1970s, after the discovery of unusual "cannibalistic" giant cells in the bronchoalveolar lavage fluid of patients with interstitial pneumonia [154]. While case reports of interstitial lung disease in workers exposed to hard metal had been described as early as the 1940s, the connection between these atypical "giant cells" and an occupational exposure to hard metal was not made until several years later, when the presence of tungsten was identified within BAL samples of patients with confirmed giant cell pneumonitis [155].

HMLD remains a fairly rare cause of occupational interstitial lung disease, though occupational cobalt exposure is highly associated with occupational asthma, and the development of contact dermatitis. HMLD may also be significantly underrecognized. Tool sharpeners, disc grinders, diamond polishers and employees working with diamond bonded tools are all at risk of developing HMLD [151]. Unlike more traditional pneumoconiosis, no formal screening program for HMLD exists, and much of the occupational exposure associated with HMLD is seen in smaller employers, or in self-employed workers [152, 156].

In one of the largest studies of workers at risk for HMLD, 2.6% of workers were found to have significant CXR abnormalities, and 10% reported work induced wheezing- an early warning symptom for both cobalt induced occupational asthma and subsequent HMLD [157]. Due to the highly soluble nature of cobalt, industrial processes such as wet cutting which are traditionally perceived as lower risk for respirable dust exposure are associated with a higher risk of cobalt exposure compared with "dry" cutting. Outbreaks of HMLD among workers exposed to these wet cutting processes have been reported even in settings where respirable cobalt measurements were significantly below the allowable limit [158].

The risk of developing HMLD appears to be largely related to host susceptibility, with some workers developing acute onset disease after minimal exposure, and others remaining disease free despite significant exposure [159]. The presence of an HLD-DPB1 glu-69 residue is associated with a significantly increased risk of developing HMLD among exposed workers [160]. Unlike chronic beryllium disease

however, lymphocyte proliferation testing has been largely ineffective in identifying sensitized workers at risk for developing respiratory disease [159].

The clinical presentation of HMLD typically begins with upper respiratory tract symptoms, including cough, throat pain, ocular irritation, and sinus drainage. With ongoing exposure, cough, dyspnea, and wheeze may develop. Systemic symptoms, including fever, weight loss and fatigue are common, and may be pronounced. Unlike the majority of other occupational interstitial lung diseases, in the early phases of HMLD, removal from exposure is associated with significant and immediate improvement. In patients for whom exposure cessation does not occur, chronic fibrotic pulmonary changes develop, similar to the clinical picture seen in chronic fibrotic hypersensitivity pneumonitis.

PFT testing in patients with early HMLD may be unremarkable, or may show evidence of obstructive physiology, with reduced DLCO [157]. Over time, restrictive changes typically develop, though patients with combined elements of occupational asthma may show a mixed PFT picture [151, 159].

Imaging patterns in early HMLD vary widely. Traction bronchiectasis, scattered ground glass opacities and air trapping are commonly reported [152]. Centrilobular and perilymphatic nodularity can also be seen, and may lead to misdiagnosis in the absence of a thorough occupational history [161].

Bronchoscopy may be performed to ascertain diagnosis. BAL fluid characteristically shows multinucleated giant cells, although the presence of these cells is not necessary to confirm the diagnosis of HMLD. Cobalt or tungsten may be identified within BAL fluid, though this is relatively rare.

Biopsy is characterized by lymphocytic interstitial infiltrate, alveolar epithelial hyperplasia and interstitial desquamation [151]. Emperipolesis, characterized by finding intact inflammatory cells within the cytoplasm of giant cells, is pathognomic for HMLD in the setting of exposure and consistent imaging findings. In advanced cases, biopsy findings may be indistinguishable from advanced fibrotic lung disease, with honeycombing and reticulation [162].

Treatment of HMLD begins with exposure removal. In patient's whose symptoms persist or worsen despite exposure removal, corticosteroid or other immunosuppressive therapy may be effective. Respirators and engineering controls should be utilized in areas where the potential for occupational cobalt exposure exists.

Potential Pulmonary Impact of Unconventional Natural Gas Development

Unconventional natural gas development (UNGD) has received increasing attention in the past decade. Also known as "fracking", UNGD is characterized by the use of hydraulic fracturing fluid to access natural gas deposits within seams of hard rock, primarily shale, coal-beds and tight sand.

The impact of UNGD on respiratory health remains largely unknown at this time, though all phases of UNGD are associated with potential exposures to

pulmonary irritants. The process of establishing a new hydraulic fracturing site begins with a pre-production period, where the land for the well-pad is cleared and transportation pathways developed [163]. This period has been associated with an increase in atmospheric $PM_{2.5}$ and PM_{10}, primarily related to diesel exhaust from heavy machinery, road dust and brake-pad debris [164]. Increased exposure to inhaled $PM_{2.5}$ and PM_{10} has previously been associated with an increased risk of respiratory symptoms and exacerbations of chronic airway disease in children and adults [165, 166].

Following pre-production, drilling begins. Once sufficient depth has been reached, the process of hydraulic fracking begins. During this process, large volumes of water, hydraulic fracturing fluid and proppant (material, usually sand, instilled to keep natural gas seams open) is injected at high pressures. Again, this process results in increased levels of atmospheric $PM_{2.5}$ and PM_{10}, along with the release of volatile organic compounds [163, 167]. The specific chemical contents of fracturing fluid varies between well developers. While mines are encouraged to disclose fracking fluid content, this disclosure is not currently mandated by law [168].

Exposure to silica contained within proppant sand is also of significant concern during the hydraulic fracturing stage. Previous studies have found that fracking workers are at risk for acute, high level silica exposure, which may not be prevented by traditional half-face mask personal protective equipment [169, 170]. Workers employed in UNGD should undergo regular silica screening, and silicosis should be considered in any patient with a history of hydraulic fracturing exposure presenting with interstitial lung disease features.

After hydraulic fracturing is completed, the process of gas venting begins. Output from UNGD wells typically slows after 2–3 years, and wells may undergo a "re-fracking" process multiple times during their lifecycle to boost production [163, 167]. During all phases of UNGD, exposure to $PM_{2.5}$, PM_{10}, volatile organic compounds (particularly benzene and toluene), and greenhouse gas emissions remains a concern.

Work into the health of residents surrounding UNGD sites is ongoing. Studies of residents in areas around UNGD sites show increased rates of self-reported respiratory and sinus symptoms [167, 171]. At a population level, periods of heavy UNGD activity are associated with an increased rate of asthma exacerbations [168]. Research into the respiratory health of UNGD workers is limited.

Occupational Lung Disease in Military Personnel and First Responders

Military personnel and first responders are at risk for a number of potential pulmonary exposures. Unlike traditional occupational lung disease evaluation, a single event may result in expected and unexpected exposures to a wide range of potentially damaging materials. Immediate environmental monitoring is rarely available,

making quantification of exposure challenging. Given this, it is important to consider a broad differential diagnosis when evaluating a symptomatic patient with an occupational history of deployment or emergency response.

Deployment Related Lung Disease

Since the early 2000s, more than 2.7 million United States service personal have been deployed to South Asia and the Middle East [172]. In addition to the potential for combat related injury, these deployments are characterized by exposure to a range of potential pulmonary irritants, including inhaled particulate matter, gas and fumes created by incineration of organic and inorganic waste [172].

Sixty-nine percent of deployed personnel report experiencing respiratory symptoms during deployment- the second most common non-combat related illness reported during deployment [173]. These respiratory symptoms are not limited to deployment- post-deployment, personnel who have been deployed continue to endorse significantly more dyspnea, wheeze and chronic cough compared to non-deployed personnel [174]. In addition to non-specific respiratory symptoms, a range of respiratory syndromes have described in personnel returning from deployment, including asthma, vocal cord dysfunction and constrictive bronchiolitis [172, 175]. Estimates of respiratory disease related to deployment are confounded by tobacco use among military personnel.

Exposure to open-air burning of waste, also known as "burn-pits" has been of particular concern. These large open air waste pits were utilized to dispose of industrial waste, plastic byproducts, human waste and solvents at a number of bases [176]. Due to the uncontrolled nature of burn-pit temperatures, breakdown of these waste products is often incomplete. Environmental air sampling in the areas surrounding a large burn-pit revealed elevated levels of atmospheric $PM_{2.5}$, PM_{10}, acrolein and benzene- all known pulmonary irritants [177]. Concern that burn-pit exposure could have long-term respiratory health impact is high among returning personnel [173]. To date, there has been no clear association between burn-pit exposure alone and risk of pulmonary disease, though there is concern that this may represent a risk factor for constrictive bronchiolitis development [173, 178].

Deployed personnel have a significantly higher risk of developing new onset asthma during deployment [179, 180]. This is theorized to be related to increased exposure to environmental $PM_{2.5}$ and other irritant particulate matter, though causal mechanisms remain not fully understood [172]. Rates of PTSD are also high within deployed personnel- exposure to increased allostatic load has also been shown to increase the risk of asthma among adolescents, and has been theorized as a potential driver of the high levels of asthma seen within this population [181]. Vocal cord dysfunction, which may mimic asthma symptoms, is also prevalent among deployed personnel- in one cohort, 6.6% of deployed personnel referred for evaluation of unexplained dyspnea were found to have vocal cord dysfunction [182].

Constrictive bronchiolitis- a disease characterized by fibrosis, narrowing and destruction of small airways, has been reported in personnel presenting with unexplained dyspnea following deployment. The largest case series identified 38 cases of constrictive bronchiolitis in previously deployed personnel referred for evaluation of unexplained dyspnea [183]. While personnel within this case series had a number of unique exposures, the majority had been exposed to high levels of inhaled sulfur due to a large sulfur mine fire in the region during the time of deployment. Cases of constrictive bronchiolitis in patients exposed to sulfur mustard have previously been reported. However, many of the identified cases had no clear sulfur exposure. Similar cases of constrictive bronchiolitis have been reported in other centers among deployed personnel, the majority of whom also lacked a clear exposure to sulfur [172, 184].

Constrictive bronchiolitis can be challenging to diagnose. PFTS are often unremarkable in the early stages of disease, though with disease progression evidence of fixed obstruction or restriction may be present [185]. HRCT imaging is also often unremarkable, though can show evidence of mosaic attenuation due to air-trapping in the fibrotic small airways [186]. Diagnosis of chronic bronchiolitis is made by surgical lung biopsy, which classically shows areas of fibrotic sub-epithelial scarring, with narrowing and obliteration of the small airways [172]. This fibrotic scarring can have significant geographic heterogeneity however, and may be easily missed [172]. Over-diagnosis is also possible due to ex-vivo contraction of smooth muscle within the bronchial wall [187]. The true incidence of constrictive bronchiolitis among previously deployed personnel remains unknown.

Tobacco use remains an under-recognized contributor to respiratory and cardiovascular morbidity among deployed personnel. 30% of US army veterans, and 14% of active duty personnel endorse active tobacco use [188, 189]. Deployment is a significant risk factor for initiation of tobacco use, and of smoking recidivism [190].

In a patient with a history of deployment who presents with unexplained dyspnea, evaluation should begin with a thorough history, including deployment history and length, occupation while deployed, and history of exposure to burn pits, dust storms or other atypical exposures. Pulmonary function testing, including spirometry with bronchodilator testing, DLCO and lung volumes is recommended as part of initial evaluation, along with high resolution CT chest imaging [175]. Of note, because the deployed population is on average, healthier than the non-deployed population, PFT testing should be carefully interpreted. Pulmonary function testing was within normal limits in many of the patients subsequently diagnosed with constrictive bronchiolitis, though lower than the values seen in healthy deployed personnel [183].

If pulmonary function is within normal limits, provocation testing to evaluate for asthma should be performed. Given the high prevalence of vocal cord dysfunction, laryngoscopy is also often recommended [175, 182]. For those in whom initial evaluation is unremarkable, cardiopulmonary exercise testing may be considered.

Whether to proceed with surgical lung biopsy should be considered on a case-to-case basis. While this may have utility in diagnosing constrictive bronchiolitis, due

to challenges in making the diagnosis even with tissue sampling and lack of consensus into the relationship between constrictive bronchiolitis and deployment, overall benefit to the patient may be low [175].

World Trade Center Associated Lung Disease

While we commonly consider occupational lung diseases from the standpoint of ongoing long-term exposures, public health disasters or mass exposure events, such as the world trade center (WTC) disaster on September 11th 2001, have been associated with a wide range of occupational sequelae, spanning from reactive airway syndromes to chronic fibrotic lung disease.

The collapse of the WTC resulted in the release of large volumes of suspended dust and smoke, comprising of a mix of gypsum (a mix of silica, calcium carbonate and sulfates), asbestos from building insulation, and volatile organic compounds released from burning jet fuel [191, 192]. This initial dust cloud was strongly alkaline, and persisted for several days as a result of ongoing fires within the site of the initial collapse.

Multiple worker groups were exposed to the immediate and moderate term effects of the WTC collapse, including paramedics, firefighters and local disaster coordination teams [191]. Residents of the area surrounding the collapse, and nearby office workers also had significant exposure [15].

A range of health conditions have been associated with exposure to the WTC collapse, and more continued to be identified. From a respiratory standpoint, cough and upper respiratory tract symptoms were some of the most commonly reported symptoms immediately following the event, with approximately half of firefighters involved in the response to the WTC collapse reporting daily cough in the first year post event [192, 193]. Wheeze and dyspnea were also common, with a high incidence reactive airways disease diagnosed in the immediate aftermath of the event. Many first responders have evidence of chronic respiratory sequelae as a result of this exposure—a significant increase in the prevalence of asthma diagnoses among firefighters was noted in the years following the collapse [194, 195].

Granulomatous disease with the potential for multi-organ involvement has been reported in WTC responders [196, 197]. An increased risk of sarcoidosis has also been identified in residents surrounding the WTC collapse [15]. Cases of idiopathic pulmonary fibrosis (IPF) have also been identified among WTC responders [198].

Evaluating and Managing Occupational Exposures

Identifying a potential link between workplace exposure and disease requires a high index of suspicion. In patients presenting with symptoms that may have a link to the workplace, a thorough occupational history is essential to identify potential exposures.

Table 5 Key elements of the occupational history

Identifying exposure:	Detailed history of current and previous employment, including specific job duties and roles Detailed history of hobbies and other environmental exposures (housing, pets, etc.) History of known exposure to agents associated with occupational lung disease Participation in previous worksite screening or surveillance programs Clusters of illness among co-workers or community members
Quantifying exposure:	Duration of time in each job role/title Single exposure versus ongoing Percent of time exposed while at work Route of exposure (inhaled, ingested, dermal) Protective factors (PPE, engineering controls)
Timing of exposure:	Temporal relationship with exposure and onset of symptoms Improvement in symptoms with exposure removal

The history include an assessment of workplace, home, and recreational exposures. Current as well as past exposures should be assessed, with specific information collected regarding job titles and job tasks at each place of employment. The presence of respiratory symptoms among co-workers or individuals with similar exposures provides further evidence for disease. Many occupational lung diseases have a long lag time between exposure and development of symptoms- because of this, reliance should not be placed on descriptions of acute symptoms during initial exposure. Use of personal protective equipment and environmental controls such as local exhaust ventilation should be ascertained. (Table 5)

For some exposures including coal, beryllium, respirable crystalline silica and asbestos, OSHA mandates for exposure assessment in the workplace may already be in place. Exposure can be assessed in a multitude of ways, including average exposures over the work day such as an 8-hour period—referred to as permissible exposure limits (PEL) or short-term exposure limit. Quality of exposure monitoring may vary, and average exposure estimates may not capture short term, high level exposures. In addition to OSHA mandates, NIOSH also publishes exposure level recommendations, known as RELS or recommended exposure limits. The American Conference of Governmental Industrial Hygienists also publishes recommendations regarding threshold limit values, which offer detailed guidance into occupational safety measures. It is important to recognize that for some occupational exposures, a true "safe" exposure limit may not exist. For diseases such as occupational asthma and FHP which develop in response to exposure to a sensitizer, disease can occur even with low level exposures.

For exposures known to cause occupational lung disease, mandatory workplace surveillance may already be in effect. These mandatory surveillance programs may comprise of a mix of symptom screening, spirometry, and chest imaging. Workplace surveillance allows for early detection of disease- decreasing the risk of progression

for impacted workers and identifying risk for other workers. Worker participation is not compulsory however, and quality of workplace spirometry may vary.

The "healthy worker" effect is an important consideration when interpreting workplace spirometry surveillance data. Those in the workforce may have supernormal FEV1 and FVC values when compared with the overall population [199]. Evidence of a longitudinal decline in FEV1 or FVC should prompt concern for occupational lung disease, even if the values remain within a "normal" range. It is also important to recognize that workplace spirometry offers a snapshot of respiratory health. For diseases with a primarily restrictive process, full pulmonary function testing including DLCO and lung volumes may be necessary.

Many diseases of the workplace have a long latency. For that reason, ongoing medical surveillance should be considered even after retirement or change in occupation, though is not readily available. Former worker screening programs exist in some industries- for example, beryllium exposed workers who were employed by the Department of Energy are eligible for lifelong screening for beryllium related complications [199]. Similarly, retired miners are eligible for ongoing screening for CWP through the NIOSH Coal Workers Health Surveillance Program [200].

Occupational lung disease surveillance relies heavily on CXR imaging. The International Labor Organization produces a CXR classification system which is widely utilized in the diagnosis of pneumoconicosis [201]. HRCT is generally not part of routine surveillance, but may be indicated when concern for disease is high. It is important to highlight that biopsy is generally not required for the diagnosis of occupational lung disease, though may occasionally be required to confirm a diagnosis.

Evaluation of sentinel cases of occupational lung disease often requires a multidisciplinary collaboration between academia, industry and government agency. In patients presenting with symptoms and an unknown exposure, safety data sheets (SDS) can provide information about potential agents the worker may have been exposed to. If there is concern that multiple workers have been impacted, an employer, employee or union official can request a NIOSH Health Hazard evaluation of the workplace. For employers wishing to evaluate their own workplace safety practices, OSHA provides a free consultation service. OSHA consultation is not associated with OSHA enforcement and will work with an employer to identify and remediate potential hazards. It is critical to remember that regulatory limits do not exist for many exposures or sensitizers. Hence public health experts must remain cognizant of the potential for the presence of workplace toxicants and continue to advocate for exposure mitigation as well primary and secondary prevention through monitoring and surveillance programs.

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Environmental and Pollution Related Risks for Hypersensitivity Pneumonitis

Vincent Ferraro and Julie Morisset

Overview of Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an immune-mediated inflammatory lung disorder resulting from repetitive inhalation of causative antigens in sensitized and genetically predisposed individuals. A subset of patients with HP will exhibit a progressive fibrotic phenotype associated with fibrotic lung disease, accelerated decline in lung function and increased mortality [1, 2]. HP should be considered as a potential diagnosis in every patient with newly detected interstitial lung disease (ILD). Antigen identification occupies a central role in the early diagnosis of HP and remains the cornerstone treatment [3, 4].

This chapter provides the reader with an overview of HP, its clinical manifestations, diagnosis and management. It also covers antigen identification methods and environmental exposure assessment. Finally, the role of air pollution and related environmental risk factors will be explored.

Epidemiology

The prevalence and incidence of hypersensitivity pneumonitis varies greatly between countries as they are influenced by numerous factors such as type and intensity of antigen exposure, climatic and geographical differences, local customs and occupational practices, all closely associated with the environmental nature of the disease. The important variations in epidemiological studies may also result

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from the lack of uniform and widely used HP diagnostic criteria [1, 5]. Although the global prevalence of HP is estimated to be low, the actual burden may be underestimated as milder forms may be missed or misdiagnosed as viral illnesses, asthma or other interstitial lung diseases (ILD). Distinguishing HP from other ILD such as idiopathic pulmonary fibrosis (IPF) may be clinically challenging especially in advanced fibrotic HP, as demonstrated in a case-cohort study where 43% of patients with an initial diagnosis of IPF where subsequently diagnosed with chronic HP through further investigations and follow-up questionnaires [6, 7].

A recent U.S administrative claims-based cohort analysis from Evans et al., established a 1-year prevalence rate ranging from 1.67 to 2.71 per 100,000 persons and a 1-year cumulative incidence rate ranging from 1.28 to 1.94 per 100,000 persons. The prevalence increases with age, particularly in individuals over 65 years old, situating itself at 11.2 per 100,000 persons, supporting the expanding evidence of aging-related mechanisms in the pathobiology of HP. Surprisingly, 58% of cases were found among women, conflicting with previous studies showing a predominance of male patients. These data may reflect a change in occupational practices, higher use of healthcare or differences in disease susceptibility [8–10].

In various multicenter prospective ILD registries, IPF and sarcoidosis diagnosis accounts for around 50% of cases, whereas the prevalence and incidence of HP represents 3–13% of ILD subtypes [10–12]. A recent study in a multi-ethnic county of the Greater Paris demonstrated similar findings, where HP comprised only 3% of ILDs of known causes [13]. In comparison, HP is the most common new-onset ILD in India accounting for 47% of new cases, which may support the impact of geographic differences as well as environmental and cultural factors on HP pathogenesis [14].

Historically, epidemiological data on HP were mainly derived from studies on farmer's lung and bird fancier's disease. The prevalence of farmer's lung is believed to range from 10 to 200 per 100,000 persons in different zones of England and Finland and between 4 and 170 per 1000 farmers in France and the United States [1, 15]. Bird fancier's disease is believed to be the most common form of HP worldwide, representing 66–68% of all HP forms. Its prevalence ranges from 500 to 20,000 per 100,000 individuals at risk, varying greatly between studies depending on the type of exposure and bird species [16, 17]. Although extremely rare, HP has been described in children with bird fancier's lung being the most frequent form [18, 19].

Pathophysiology

The pathogenesis of HP revolves around an immune-mediated inflammatory reaction of the lung parenchyma resulting from recurrent inhalation of environmental causal antigens in genetically predisposed sensitised individuals. Causative antigens include a wide range of organic and inorganic particles sufficiently small to reach the lung alveoli (<5 μm) [20, 21]. The immunopathogenesis of HP is similar

regardless of the antigen type [22]. HP is believed to results from a complex interaction of individual host susceptibility factors and inducing environmental exposures which may explain the relatively low incidence of the disease, despite worldwide distribution of causal antigens in all aspects of life [23, 24]. When exposed, most individual will remain asymptomatic and develop, at worse, a mild lymphocytic alveolitis triggered by regulatory T cells (T_{reg}) suggesting the development of an immune tolerance to the antigens [2, 17].

Genetic factors determining HP predisposition remain unclear, although emphasis has been placed on the major histocompatibility complex due to its role in immune response regulation. Polymorphisms in Class II MHC molecules have been associated with a higher risk of HP [20, 21, 25]. Cohorts of familial HP have been described primarily in Japanese summer-type HP, although familial hypersensitivity to bird antigens has also been reported [26–28]. Furthermore, a retrospective review of patients with chronic HP (cHP) demonstrated that 17.5% of patients had a family history of pulmonary fibrosis, reinforcing the role of genetic predispositions in the development of HP [29]. The exact mechanisms leading to fibrotic HP remain unclear, although Barrera et al. indicated differences in phenotypic and functional T cells subtypes when comparing chronic to subacute HP [30]. In addition, recent studies have demonstrated an association between MUC5B polymorphism and the extent of fibrosis in cHP, as well as the role of telomere shortening and dysfunction in the fibrotic pathogenesis of cHP and its negative impact on survival [31–33].

Etiology

The repertoire of causative HP antigens has been ever growing in recent years with over 200 identified antigens. The inciting agents include bacteria, mycobacteria, fungi, animal and plants proteins, metal and low-molecular-weight chemical compounds [16, 34, 35]. Previously described as an occupational disorder based on HP prototypes such as farmer's lung, the number of home and recreational HP-associated settings have been growing continuously [36–39]. At risk work environment include among others farming, bird breeding and metal working whereas non-occupational settings such as hot tubs, contaminated humidifiers and water damaged homes have been associated with HP [5]. A recent systematic review of literature by Barnes et al., identified birds as the most common exposure in HP, occurring in 25% of cases, followed by mold and farming [40]. The term cryptogenic HP has been used to describe well defined HP showing clinical, radiological and histopathological signs of the disease in which the inducing agents remains unidentifiable. These situations are frequent and were reported in up to 30–60% of cases. Patients with cryptogenic HP tend to present a more chronic course, similar to IPF, and may have a worse prognosis as the inability to identify an inciting agent is associated with shorten survival in patients with cHP [16, 23, 41]. Causative antigens as well as environmental exposures and related risk factors will further be discussed in the second portion of this chapter.

Clinical Manifestations

Clinical manifestations of HP are generally similar regardless of the inducing agent. The time interval between onset of symptoms following sensitization by antigen inhalation appears to be extremely variable and may begin only months to years after exposure. Historically, the clinical presentations of HP were divided as acute, subacute or chronic based on the frequency, intensity and duration of antigen exposure as well as the duration of illness. However, these classical subcategories may easily overlap as the clinical presentations are heterogeneous and reflect little prognostic value [5, 23, 42]. With growing evidence associating radiological and histopathological signs of fibrosis to a generally poor prognosis in HP, a new classification of HP as acute/inflammatory or chronic/fibrotic HP based on clinical, radiological and histological data integration was suggested and recommended in the new HP guidelines [4, 23, 43, 44].

In the acute HP form, symptoms generally occur in the hours following causative antigen exposition and most frequently consist of flu-like symptoms including fever, malaise and chills. Pulmonary symptoms include severe dyspnea, chest tightness, dry or mildly productive cough and in rare circumstances hemoptysis. Diffuse crackles and tachypnea may be observed in all HP forms. Symptoms commonly resolve over hours to days and may reoccur following subsequent expositions [2, 5]. Unrecognized as well as recurrent untreated acute HP may progress to chronic HP, although some patients may present with an insidious and progressive onset of symptoms, lacking noticeable acute episodes which may be mistaken for other interstitial lung diseases such as IPF. This presentation is frequently seen in patients exposed to avian antigens, as patients may inhale persistent low-level of antigens in the domestic setting. Fibrotic HP is characterized by a progressive dyspnea, cough, fatigue, malaise and weight loss. In advanced disease, digital clubbing may be present and may help predict clinical deterioration [2, 5, 45].

Investigations

High-Resolution Computer Tomography (HRCT)

HRCT is the preferred imaging method for ILD and HP as it provides a superior assessment of the type, extent and distribution of disease, and correlates better with clinical and functional parameters [5, 46–48]. Nevertheless, some patients with proven HP may present with normal HRCT as shown by Lacasse et al. [49, 50]. In non-fibrotic HP, the typical radiological patterns consist mainly of a combination of parenchymal infiltration (e.g. ground glass opacities, mosaic attenuation) with HRCT signs of small airway disease (e.g. ill-defined centrilobular nodules, air trapping) with a diffuse distribution [4, 23, 51]. In fibrotic HP, HRCT findings include signs of fibrosis such as reticulation, architectural distortion and traction bronchiectasis with or without honeycombing, combined with signs of small airway disease (centrilobular nodules, ground glass opacities, mosaic attenuation or air trapping)

[4, 23, 52–54]. Radiological features that may help better differentiate fibrotic HP from IPF) include the presence of lobular areas with decrease attenuation, air trapping, centrilobular nodules and the lack of lower zone predominance, as IPF generally presents with a basal predominance. Specific HRCT findings allow confidence distinction of fibrotic HP from IPF in approximately 50% of cases [2, 53]. The head cheese sign or three-density pattern refers to the juxtaposition of ground glass opacities, mosaic attenuation and normal lung tissue with abrupt margination and is believed to be relatively specific for fibrotic HP [4, 55, 56].

Pulmonary Function Tests

Pulmonary function tests (PFT) are useful to determine the severity of lung function impairment at diagnosis and follow-up. No abnormalities are specific or diagnostic for HP, as similar findings are found in other ILDs. A restrictive ventilatory defect is generally observed with decreased lung volumes and reduction in carbon monoxide diffusing capacity (DLCO) [2, 5]. Hypoxemia resulting from impaired gas exchange may be observed. Patients in early mild to moderate stages of the disease may be normoxemic at rest but will become hypoxemic with exertion as shown with a 6-minute walk test (6MWT). Correlation between PFT abnormalities and the severity or prognosis of HP is poor as some patients with severe pulmonary function abnormalities may completely recover while others with mild impairment may progress to develop fibrosis, although low forced vital capacity (FVC) and DLCO at baseline as well as significant decline occurring within the first year of the disease have been shown to be predictive of mortality [5, 57–59].

Bronchoalveolar Lavage (BAL)

Bronchoalveolar lavage is a highly sensitive method at identifying alveolitis in patients suspected of having HP. A significant increase in total cell count as well as a marked lymphocytosis, often exceeding 50%, is particularly suggestive of HP, albeit a threshold that distinguishes HP from other ILDs with both high sensitivity and specificity remains controversial [2, 42, 59, 60]. BAL lymphocytosis is also reported in other granulomatous lung diseases such as sarcoidosis or cryptogenic organizing pneumonia, as well as NSIP, although generally to a lesser extent [61]. The presence or absence of significant lymphocytosis may help distinguish fibrotic HP, especially in the context of a usual interstitial pneumonia (UIP) pattern, from IPF patients who generally present with levels similar to those of healthy control subjects [23, 62, 63].

Furthermore, an elevated BAL lymphocytic content may be observed in asymptomatic individuals with antigen exposure and may simply represent a low-intensity alveolitis with no significant long-term consequences [64]. HP patients who smoke show lower BAL lymphocyte count compared to non-smokers [50]. The evaluation of T cell subsets is no longer supported as expanding evidence suggest that T cell

subsets and CD4+/CD8+ ratio vary in relation to a multitude of factors and that a low CD4+/CD8+ ratio, although suggestive of HP, is insensitive and nonspecific [23, 61].

Histopathology

The classic histopathologic triad in nonfibrotic HP includes cellular interstitial pneumonia, cellular lymphocyte predominant bronchiolitis and poorly-formed non-necrotizing granulomas [4]. A large retrospective series by Castonguay et al. identified this classic triad in 73% of patients with HP [65]. Histopathological criteria for the diagnosis of fibrotic HP require the combination of chronic fibrosing interstitial pneumonia, airway centered fibrosis and poorly-formed non-necrotizinf granulomas [4, 66]. Important pathological features in differentiating fibrotic HP with a UIP-like pattern from IPF include the presence centrilobular fibrosis and bridging fibrosis, which are important hallmarks of fibrotic HP [67, 68].

Diagnostic Criteria

Diagnostic criteria for HP have evolved over recent years leading to the publication of 2 guidelines in the past year: the official ATS/JRS/ALAT Clinical Practice Guideline on the Diagnosis of Hypersensitivity Pneumonitis in Adults and the Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guineline and Expert Panel Report [4, 69]. Although there are some differences these documents, they both agree the diagnosis of HP requires proper integration of multiple domains including clinical, radiological and histopathological data, ideally considered in the context of an ILD multidisciplinary team meeting (MDTM). Inter-MDTM agreement for the diagnosis of HP remains low as demonstrated in a case-cohort study by Walsh et al. [70]. No feature is sufficient in itself nor are any mandatory for the diagnosis of HP. If all features are typical for HP including an identified exposure, a typical HRCT pattern and a BAL lymphocytosis, the diagnosis can be made without the need of a lung biopsy. In all other combinations of findings, when a high-confidence diagnosis cannot be achieved, histopathology specimen should be obtained [4].

Treatment

The mainstay treatment in HP consists in antigen remediation. Early and complete avoidance of the inciting agent may lead to disease regression in acute symptomatic disease, although patients may still present with adverse outcome following avoidance [5, 23, 71]. In patients with fibrotic HP, the identification of a causative antigen is associated with improved survival when adjusting for potentially influencing

factors [41]. Early HP diagnosis, antigen identification followed by removal are essential as prolonged exposition is associated with a reduction in pulmonary function recovery following antigen avoidance [72]. Proper antigen removal methods are still to be determined and remain a challenge. High level of avian antigen may be detected for months following bird removal and professional environment cleanup [73]. Drastic measures such as home relocation or career reorientation are sometime necessary [74, 75].

Corticosteroids are recommended in acute symptomatic HP, as well as severe and progressive disease [5, 23]. Long-term outcome in non fibrotic HP appears unchanged by corticosteroids as demonstrated in a trial on acute farmer's lung patients where pulmonary function improved after 8 weeks of prednisolone when compared to placebo but no change on long-term pulmonary function were noted [76]. In similar fashion, Mönkäre demonstrated faster symptoms resolution in patients treated with corticosteroids than antigen avoidance alone, although no differences in long-term clinical course or pulmonary function after 6 months [77]. Efficiency of corticosteroids in chronic fibrotic HP remain to be determined, albeit often used. A recent study by De Sadeleer et al. showed no therapeutic effects of corticosteroids in fibrotic HP [75]. Azathioprine (AZA) and mycophenolate mofetil (MMF) may be used in chronic HP. Both AZA and MMF were shown to improve DLCO in patients with fibrotic HP and have fewer adverse events than corticosteroids, suggesting an early transition may be appropriate [78, 79].

Recent studies have suggested the use of antifibrotics in fibrotic HP. The antifibrotic agent nintedanib has been shown to slow pulmonary function decline in idiopathic pulmonary fibrosis, considered the prototype of progressive fibrosing lung diseases [80–82]. The INBUILD trial compared nintedanib to placebo in 663 patients with progressive fibrotic lung disease other than IPF, of which 26% had fibrotic HP. Nintedanib was associated with a significantly lower rate of FVC decline, attesting to its possible benefits in chronic fibrotic HP, although the study was not designed to provide evidence for benefits in specific diagnostic subgroups [83, 84]. Furthermore, a retrospective real-life observational study by Tzilas et al. showed significant reduction in FVC and DLCO decline over a 3-year period in patients with fibrotic HP receiving either nintedanib or pirfenidone, however randomized trial extending over more than 1 year are necessary to evaluate their long-term efficiency [85].

Lung transplantation may be required in advanced forms of HP. Post-transplant medium-term survival is superior than in patients with IPF [86]. Aggressive antigen avoidance is necessary following lung transplant as ongoing antigen exposure may lead to recurrence of the disease in the allograft despite standard post-transplant immunosuppression [87].

Prognosis

Long-term prognosis in HP is variable and depends on numerous factors including duration of exposure, type of antigen as well as inter-individual immune response. Factors associated with worst outcomes include prolonged or greater intensity of exposure, older age, histologic patterns of fibrotic NSIP or UIP and digital clubbing [44, 45, 59, 72, 88–93]. Furthermore, extensive traction bronchiectasis on HRCT strongly predict poor survival in chronic HP [43]. Episode of acute exacerbations also negatively influence disease evolution [94]. In addition, the type of antigen may also impact the prognosis as bird fancier's lung generally shows poorer outcomes when compared to farmer's lung, which may result from higher level of antigen exposure as well as persistent and difficult to eradicate avian household exposition [73, 95]. Fernandez-Perez et al. demonstrated a mean survival time in fibrotic HP of 8.75 years when the inciting antigen was identified compared to 4.88 years in cases of nonidentification, urging the importance of proper antigen identification in HP [41].

Environmental Exposure and Influence of Pollution

Antigen Identification

As previously stated, causative antigen identification occupies a fundamental role in the diagnosis of HP, which remains challenging given the heterogeneous presentation of the disease and its overlapping features with other ILDs [4]. Moreover, early identification of possibly inducing agents is essential for proper remediation of exposure, in ways to limit progression and favorably impact prognosis [23, 41, 71]. Multiple tools have been developed over the years to better assess possible causative antigens, although limited evidence exists on their proper use in the clinical setting [96]. Failure to identify an inducing antigen remains frequent and is estimated to occur in 30–60% of cases [16]. A large claim-based cohort analysis of HP in the United States estimated that nearly 40% of patients with suspected HP presented with no identifiable antigen [8]. The causality between an exposure and the disease can be evident in cases of occupational HP, however domestic exposures may often be occult making antigen identification challenging [6].

A detailed clinical exposure assessment is an essential component of the clinical history in patients with suspected HP and should be revisited during follow-up visits. On the occasion that a well-defined causative antigen is identified during the clinical history, further testing in regard to antigen identification may not be required. Furthermore, questionnaires may allow a more exhaustive and consistent evaluation of possible exposures, although none have been validated [97]. Questions should be relevant to the regional patient population and consider temporality of exposition [97]. However, limited agreement exists on which type of exposures

should be more particularly questioned during clinical history. A Delphi assessment of 36 international ILD experts conducted by Barnes et al. found consensus on 18 exposure items to ask every patient with suspected HP. The 5 elements with the highest agreement include exposure to moldy hay or silage, standing water, water damage or flooding, visible mold or a moldy smell and bird or avian protein exposure [98, 99]. In some cases, the involvement of an industrial hygienist or exposure scientist may be beneficial in identifying unrecognized exposure as well as offering tailored advices on how to reduce antigen exposure in the home and or workplace [97].

Specific antibodies against a possibly causative antigen are often detectable in HP, although their clinical relevance is controversial as they may be found in asymptomatic exposed individuals. The presence of antibodies solely denotes sensitization to an exposed antigen and between 10% and 50% of asymptomatic exposed individuals present with detectable antibodies [2, 5, 100, 101]. The incidence of positive antibodies in asymptomatic pigeon breeders is greater than in farmers and may be explained by more intense and prolonged exposition to causative agents. A series on bird fancier's lung (BFL) by Morell et al. demonstrated that 92% of patients with BFL had positive antibodies as well as 87% of pigeon breeder controls [5, 102]. Nonetheless, presence of antibodies in an appropriate clinical setting supports the diagnosis of HP. Serology assays for specific antibodies may help establish a relationship between an exposure and the disease or screen for potential inducers when clinical data and HRCT are compatible with HP but the causative antigen remain undetermined [23]. The selection of antigens to be tested should depend on personal exposure history and regional prevalence of exposures [16, 23, 103, 104]. Routine IgG testing of all patients with suspected HP with broad antigen panels may help warn physicians of possible exposures that were not initially considered, although limited data exist on this type of approach [97, 104, 105].

Currently, physicians do not easily have access to individualized panels based on patient's environment [16, 106]. A proof of concept study by Millrick-May et al. attempted to determine whether a site visit and sampling of a patient's home and or workplace would be effective at identifying causative antigens in patients with HP. Out of the 19 individuals, 7 had positive IgG to environmental samples, while 12 out 19 had positive results to the standard HP panel. Among the 6 individuals who reacted to the standard and environmental panel, only one patient reacted to the same antigen. A clear benefit of a patient-centered environmental assessment includes the possibility to provide feedback to the clinician as to potential exposures and help interpret commercial HP panels. An absence of response to environmental samples from the home or workplace combined with positive results on a standard panel most probably suggests that the patient is no longer exposed to the causative agent. In addition, individualized environmental panels may enable clinicians to have hands-on discussions with their patients on specific locations where the antigenic agent may be found and allow for individualized recommendations for exposure remediation and avoidance [106].

Inhalation challenge is a third method that may be used for antigen identification as it may help confirm the causality between a possible inducing agent and the disease and can be performed by natural environmental exposure or by inhalation of a suspected antigen in a laboratory-controlled setting [16, 23, 107]. Specific inhalation challenges have shown good diagnostic performance with a sensitivity and specificity, respectively of 73% and 84% and even greater in cases of avian or fungal antigens situating itself at 85% and 86% as reported by Muñoz [108]. However, multiple obstacles to the frequent use of inhalation challenges remain. When evaluating the clinical applicability of exposure assessment tools in HP, specific inhalation challenge was rated as of poor feasibility by twenty independent experts due to its limited role and requirement of experienced laboratories. In addition, the test's accuracy in identifying causative antigens remains to be determined [97]. Considering the lack of standardization as well as the possibly harmful and unpredictable responses, inhalation challenges should not be routinely performed and should be intended for situations where other investigative measures are inconclusive [5, 23, 109–111, 103, 112].

Antigen identification remains complex and time consuming. No exposure assessment tools readily enable clinicians to identify causative antigens in all cases [97]. Additional data is necessary to properly standardize these investigative measures. At present, detailed clinical histories and questionnaires tailored to the regional patient population occupy a pivotal role in the evaluation of patients with suspected HP.

Causative Antigens

Farmer's Lung

Farmer's lung disease (FLD), often considered to be the HP prototype, is one of the most studied and prevalent types of HP. It results from inhalation of microorganisms of hay and dusts from grain or straw stored in very damp conditions in agricultural yards [16, 113, 114]. The most common causative antigens in FLD are bacteria of the specie *thermophilic actinomycetes,* such as *Thermoactinomyces vulgaris*, *Thermoactinomyces viridis*, *Thermoactinomyces sacchari* and *Saccharopolyspora rectivirgula* [114, 115]. These microorganisms generally reproduce in high humidity environments at temperatures of 40–60 °C, thus thriving in contaminated farms and agricultural yards [5, 114]. Certain farming conditions may heighten the risk of developing FLD as they may be associated with higher levels of *thermophilic actinomycetes* in the air. The number of spores is higher in large cylindrical bales of hay in comparison to small prismatic bales. Furthermore, farming practices such as manual handling of hay or the continual presence of hay in the feeding corridors increases the spread of spores [5, 116]. Farmers working in poorly ventilated environments and improperly protected could inhale around 750,000 actinomycetic spores per minute [5, 117]. FLD may also result from exposition to fungi including

Alternaria, *Aspergillus fumigatus* and *Botrytis* [16, 114, 118]. In addition, *Absidia corymbifera*, *Eurotium amstelodami*, and *Wallemia sebi* were identified as the main causative antigens of FLD in France. Reboux et al. demonstrated that the methods used to make hay appeared to be the major factor influencing its microbiology when comparing samples from farms in Finland and France [119]. FLD predominates during the winter season where hay is stored in greater quantity as well as during periods of excessive heavy rainfalls [120]. Gradual change in farming methods and rise in adequate prevention methods have led to a decline in FLD when comparing the incidence rates from 1982 to 1996 and 1997 to 2002 in Ireland [5, 121, 122].

Bird Fancier's Lung (Avian Antigens)

Bird fancier's lung (BFL) is the most common type of HP worldwide and results from inhalation of avian antigens including bird feathers, droppings and secretions [16, 17, 123, 124]. Inhalation of avian antigens from duvets, pillows or cushions filled with goose or duck feathers may lead to feather duvet lung, a more novel subgroup of BFL [17, 125–127, 128, 129]. BFL is generally associated with birds from the *Psittaciformes* order including parrots, budgerigars and cockatoos as well as pigeons or doves. Some cases of BFL have also been reported with exposure to poultry including chicken, turkey, geese and ducks [16, 17, 102, 130, 131]. Furthermore, levels of avian antigens have been associated with disease progression and prognosis in chronic BFL [90]. The periodicity often found in farmer's lung is absent in BFL. As previously mentioned, BFL holds a worst prognosis when compared to FLD which may be due to higher levels of antigen exposure combined with difficult to eradicate avian exposition, which may require in some cases a temporal household relocation [17, 75, 95].

Metalworking Fluid HP

Metalworking fluid (MWF) are used in multiple industries to facilitate the manufacture of metal components by decreasing the heat from the tools and products being made. MWF can be pure petroleum oils, semi-synthetic fluids or synthetic fluids [89, 132, 133]. The recirculation of these products may become contaminated by microorganisms despite the addition of biocides. Contamination may occur from environmental sources or from the workers' flora [89, 134]. MWF HP has been reported in workplaces with MWF containing nontuberculous mycobacteria (NTM), the most frequent being *M. immunogenum* [5, 135]. Wallace Jr. et al. demonstrated the presence of *M. immunogenum* in 102 of 107 isolates of MWF in 10 industrial sites within the United States and Canada with reported cases of HP [136]. Other NTM have been identified in MWF such as *M. chelonae* or M. *abscessus* [137, 138]. MWF HP may also occur in mycobacteria free workplaces. MWF may be

contaminated by bacteria such as *Pseudomonas pseudoalcaligenes, Pseudomonas nitroreducens* and *Ochrobactrum anthropi* among others [134, 139, 140]. In regard to MWF screening, DNA-based protocols may permit efficient screening of MWF samples in the workplace [140–142]. Occupational exposures to MWF are frequent with over 1.2 million individuals working in various metalworking operations [5, 143]., Furthermore, Barber et al. estimated that MWF is the most frequent causative agent in occupational HP in the United Kingdom over the last 20 years, urging the need for proper prevention and identification of MWF HP [144].

Hot Tub Lung

Hot tub lung is a type of HP believed to result from the inhalation of non-tuberculous mycobacteria (NTM) from water aerosol in enclosed hot tubes, home saunas and indoor swimming pools, although outdoor water recreational facilities have also been reported [145–148]. The NTM typically identified in cases of hot tube lung is *M. avium* complex (MAC) [5, 149–152]. NTM are frequently found in hot tubs and warm water pools as demonstrate by Glazer et al. where 13 out 18 random air and water samples from public water facilities were shown to have *M. avium* and NTMs. Use of halogen (chloride or bromine) as well as higher water turnover rates were associated with lower NTM levels [153]. Important risk factors for mycobacteria exposure at spa facilities include poor ventilation, wet storage of filters and water aerosolisation during cleaning of filters such as the use of pressure washers. Aerosol producing cleaning procedures should be avoided on pool equipment likely to carry mycobacteria [154].

Fungal Exposure

Fungal or mold exposure represent an important cause of HP and can be found in various occupational and home settings. Fungi associated HP have been reported with humidifiers, also known as humidifier's lung, as well as heating and ventilation systems contaminated *Aspergillus, Cladosporium, Penicillium, Aureobasidium pullulans, Cephalosporium, or Mucor* species [16, 155–157]. Ordinary domestic exposure to mold may lead to fungal related HP and should always be considered, particularly when the history reveals residential water-damage or in the absence of an apparent causative antigen [158–163]. Furthermore, as previously mentioned, farmer's lung may result from fungi exposition [118]. A multitude of other HP associated fungal exposures exist and have been described over the recent years such as in woodworkers in sawmills exposed to woods colonized by fungi, among others [16, 164–166].

Summer-type HP (SHP) is the most frequent type of HP in Japan as demonstrated by an epidemiological study performed in the 1980s where SHP represented 74.4% of HP cases. The causative antigens in SHP are the fungi of the *Trichosporon*

species, typically *Trichosporon cutaneum* which generally occurs in wooden homes during periods of high humidity and temperature [16, 167, 168].

Chemical Exposure

Occupational HP, and in some rare cases non-occupational HP, may result from the inhalation of low molecular weight (LMW) chemical compounds [88, 169, 170]. Seed et al. demonstrated, in a recent study, that HP causing chemicals tend to have a higher protein cross-linking potential, lipophilicity as well as predicted asthma hazard when compared to chemicals capable of inducing occupational asthma [169]. Synthetic LMW chemicals may form bonds with proteins and lead to dysfunction of the immune system in predisposed individuals [169, 170].

Isocyanates are a known compound capable of inducing HP and are often used in the manufacturing of paints, adhesives and foams. Multiples cases have been reported in spray painting and plastic industries [16, 171–175].

Anhydrides are also associated with occupational HP and exposure to these LMW compounds can be found in numerous industries including paints, plastics and glues and epoxy resins [16, 176, 177].

Environmental Associated Risk and Protecting Factors

Air Pollution

Ambient air pollution is an important contributor to the world global disease burden. Air pollutants levels have increased in urban areas over the past 25 years. At present, over 90% of the world population lives in areas where the daily ambient air pollution exceeds the recommendations by the World Health Organization (WHO) [178, 179]. The negative impact of air pollution and its contribution to a wide range of pulmonary diseases and systemic disorders have been well recognized, however the literature remains scarce in regard to its association and impact in ILDs despite many of them being strongly linked to environmental exposures [180–182]. Among air pollutants, particulate matter (PM), ozone and nitrogen dioxide have been strongly associated with negative respiratory outcomes [181]. PM of less than 2.5 μm in diameter ($PM_{2.5}$) can reach the lung alveoli and has been demonstrated by Lelieveld et al. to be the source of air pollution most associated with premature mortality on a global scale [183].

A recent study by Singh et al. evaluating the correlation between ambient air pollution and HP in 11 cities in urban India, identified a strong positive correlation between the percentage of HP cases and the level of $PM_{2.5}$. When adjusting for possible cofounding variables such as bird exposure, air conditioners, air coolers and molds, every increase in 10 ug/m^3 of $PM_{2.5}$ was associated with a 7% increase in the

Table 1 Summary of studies on ambient air pollution and Interstitial Lung Disease (ILD)

Study	Study Design	Study Aim	Country	Study Population	Study Findings
Studies on specific association of air pollution in HP					
Singh [184]	Prospective study from ILD registry	Determine an association between air pollution and HP	India	386 patients with HP from Indian ILD registry	Every increase in $PM_{2.5}$ of 10 ug/m^3 was associated with a 7% increase in the risk of developing HP
Studies on the association of air pollution in ILDs					
Sack [185]	Prospective cohort study	Determine an association between air pollution and ILA	USA	2671 patients from the MESA study	Odds of ILAs increased 1.77-fold per 40 ppb increment in nitrogen oxides. Ambient air pollution exposures were associated with subclinical ILD
Rice [186]	Longitudinal prospective cohort study	Determine an association between long-term exposure to traffic and ambient pollutants and ILA and progression of ILA	USA	2618 Framingham study participants	Higher 5-year average exposure to elemental carbon was associated with 1.27 times greater odds of ILAs, and 1.33 times greater odds of ILAs progression
Conti [187]	Longitudinal retrospective cohort study	Determine an association between long-term air pollution exposure and IPF incidence	Lombardy, Italy	2090 incident IPF patients	Increment of 10 $\mu g \cdot m^{-3}$ in NO_2 concentration was associated with an increase between 7.93% and 8.41% in IPF incidence rate. Potential association between exposure to traffic pollution and the development of IPF
Shull [188]	Retrospective cohort study	Cross-analysis of geographic regions of IPF cases and mapping of $PM_{2.5}$ concentration	Catalan region, Spain	379 IPF patients	Prevalence of IPF was higher in areas of high $PM_{2.5}$ concentration

Table 1 (continued)

Study	Study Design	Study Aim	Country	Study Population	Study Findings
Johansson [189]	Longitudinal prospective cohort study	Determine an association between air pollution exposure and lung function and disease severity in IPF	USA	25 IPF patients	Increased average exposures to NO_2, $PM_{2.5}$ and PM10 were associated with lower FVC in patients with IPF, although no relation between air pollution and the rate of FVC decline were objectified
Winterbottom [190]	Retrospective cohort study	Determine an association between exposures to $PM_{2.5}$ and PM_{10} and lung function decline in IPF	USA	135 IPF patients	Significant association between PM_{10} levels and the rate of decline in FVC, with each μg/m^3 increase in PM_{10} associated with an additional 46 cc per year decline in FVC
Johansson [191]	Longitudinal prospective cohort study	Determine an association between air pollution exposure and acute IPF exacerbations	South Korea	436 IPF patients	An increase in ozone (O_3) and nitride dioxide (NO_2) exposure over the preceding 6 weeks was associated with a significant increase in the risk of acute IPF exacerbation
Sesé [192]	Longitudinal prospective cohort study	Determine the impact of air pollution exposure on the natural history of IPF	France	191 IPF patients	Higher mean concentration of O_3 within the preceding 6 weeks was associated with a significant increase in the risk of acute IPF exacerbation (47% increase per 10 ug/m^3). Cumulative concentrations of PM_{10} and $PM_{2.5}$ were significantly associated with mortality

(continued)

Table 1 (continued)

Study	Study Design	Study Aim	Country	Study Population	Study Findings
Yoon [193]	Longitudinal retrospective cohort study	Determine the impact of air pollution exposure on mortality in IPF	South Korea	1114 IPF patients	Increase in NO_2 exposure can increase mortality in IPF, especially in elder men. 10-ppb increase in NO_2 concentration was associated with a 17% increase in mortality of patients with IPF
Dales [194]	Longitudinal retrospective cohort study	Determine if an acute increase in air pollution exposure is a risk factor of hospitalization in patients with IPF	Santiago, Chile	Hospitalized IPF patients in the provincial health database	Acute increases in air pollution are a risk factor for hospitalization of patients with IPF. Hospitalization of IPF patients were shown to be significantly higher the day or following days of an increase in air pollution. (Higher associations for $PM_{2.5}$ and NO_2)
Cromar [195]	Longitudinal prospective cohort study	Determine the impact of short-term exposure to air pollution on lung function in ILD	USA	1365 ILD patients	An interquartile range increase of the daily 8-hour maximum ozone (O_3) led to a significant decline in lung function (FEV1). Short-term exposure to air pollution is associated with a decline in lung function in ILD

Adapted from Majewski and Piotrowski [182]

risk of HP [184]. The risk of developing HP appears to be higher in individuals exposed to causative HP antigens who additionally live in urban cities. These findings could in part explain the significantly higher proportion of HP among new-onset ILDs in the Indian registry when compared to other countries with drastically lower levels of ambient air pollution [14, 179, 184]. The authors suggest that pollution may be a contributing factor in the pathogenesis of HP, as particulate matter may lead to

airway inflammation and reduced mucociliary clearance resulting in retention of the causative antigen in the alveoli and the subsequent immunologic response [184].

Although few studies specifically address the effect of air pollution on HP, growing evidence suggests that ambient air pollution is a risk factor for the development of ILDs and their progression (Table 1). Interstitial lung abnormalities (ILA) and high attenuation abnormalities (HAA) are radiological measurements of subclinical ILDs. Recent studies aimed at evaluating the impact of air pollution on subclinical ILDs have shown that a 10-year increase in nitrogen oxide exposure as well as a 5-year increase in element carbon exposure were associated with higher risks of ILA, thus suggesting that air pollution is associated with preclinical ILD [180, 185, 186]. In regard to IPF more specifically, which shares common pathobiological grounds with HP, Conti et al. demonstrated a potential association between traffic-related pollution and the incidence of IPF in Lombardy, Italy [187]. Similarly, a higher prevalence of IPF patients was shown in areas of the Catalan region in Spain with elevated levels of $PM_{2.5}$ [182, 188].

When it comes to the effect of air pollution on ILD progression, increased exposures to PM_{10}, $PM_{2.5}$ and nitride dioxide were associated with lower FVC in patients with IPF patients followed prospectively for 40 weeks, although no relation between air pollution and the rate of FVC decline were objectified [189]. On the contrary, a study by Winterbottom et al. showed an association between the average PM_{10} levels and FVC decline in IPF [190]. Furthermore, ozone and nitride dioxide exposure over the preceding 6 weeks were shown to increase the risk of acute IPF exacerbation, while mortality was significantly associated with cumulative concentrations of PM_{10} and $PM_{2.5}$ [191, 192]. Increased exposure to nitride oxide is also associated with a higher risk of mortality in IPF [193]. Moreover, hospitalization of IPF patients were shown to be significantly higher the day or following days of an increase in air pollution [194]. All in all, ambient air pollution is negatively associated with outcome in IPF and other fibrotic ILDs [196].

The mechanistic pathways in which ambient air pollution may contribute to the development and progression of ILDs are numerous and include oxidative stress through the production of excessive reactive oxygen species (ROS), reduced mucociliary and macrophage clearance, shortening of telomeres, dysregulated fibrogenisis as well as through epigenetic modifications [180, 181, 197].

Pesticides

Few studies have explored the potential role of pesticides in farmer's lung. When controlling for other common farming activities, the use of pesticides, more precisely dichlorodiphenyl trichloroethane, lindane and aldicarb as well as high pesticide exposure events were independently associated with farmer's lung [198].

Viral Infections

Viral infections may represent a promoting factor for in the development of HP in patients exposed to causative antigens. A study by Cormier et al. demonstrated that mice infected by Sendai virus who were simultaneously sensitized to HP antigens showed an enhanced response to the causative antigen well beyond the transient viral infection [199, 200]. Furthermore, common respiratory viruses were found in the lower respiratory tract of patients with acute HP [201]. Through its modulatory effect on the immune system which includes an increase in antigen presenting capacity of alveolar macrophages, a decrease in phagocytosis and antigen clearance, a release of pro-inflammatory cytokines as well as an increase the proliferation of Th1 T-lymphocytes, viral infection may play a triggering role in HP [200].

Table 2 Overview of preventive measures in hypersensitivity pneumonitis

	Specific preventive measures	References
Farmer's lung disease	Efficient drying or heating of the hay and cereal before storage	[114, 119, 206, 207]
	More extensive use of silage and slow emptying of silos	
	Use of loosely packed square bales	
	Mechanical feeding systems	
	Well ventilated storage areas with continuous flow system	
Metalworking fluid	Enclosing of selected metalworking fluid machineries	[89, 137, 140–142, 208, 209]
	Elimination of mist cooling	
	Exhausting additional water-based industrial processes	
	Increasing general dilution ventilation	
	Re-engineering of stations to remove recirculation circuits	
	Molecular-based screening of metalworking fluids	
	Monitoring of spatially clustered contamination for early detection	
Hot tub lung	Proper ventilation of water facilities	[154]
	Water filters should not be stored wet	
	Reduction of water aerosolisation during cleaning of filters. Aerosol producing cleaning procedures such as the use of pressure washers should be avoided on pool equipment likely to carry mycobacteria.	

Table 2 (continued)

	Specific preventive measures	References
Fungi related HP	Appropriate control of indoor moisture levels Occupied living areas should be kept with humidity levels under 60%	[210]
	Avoidance of carpets in areas of high or uncontrolled humidity	
	Rapid detection and repair of water damaged infrastructures	
	Regular maintenance of humidifiers, vaporizers, heating and air-conditionings	
	Daily empting and cleaning of humidifiers and vaporizers with hydrogen peroxide or chlorine bleach	
	Universal preventive measures	
Protective equipment: Masks and filters may help limit the inhalation of causative antigens and may be especially useful when complete eradication of an antigenic burden is not feasible. Further evidence is needed to confirm their efficiency in preventing antigen sensitization and progression of the disease Protective equipment should be chosen while taking into account the tolerability of the device in ways to maximize compliance as well as the type of environmental exposure		[114, 211–216]
Educational resources: Simply formatted educational material and worker training may help reduce causative antigen exposure. Occupational professionals may help educate employers, supervisors and workers on the importance and proper use of protective equipment		[211]
Workplace assessment: Workplace exposure assessment performed by occupational professionals can help identify at-risk workers. New occupational HP cases should lead to an assessment of the workplace as surveying the remaining workforce following a new sentinel HP case may identify additional workers affected by HP		[71, 211, 217]

Cigarette Smoking

Cigarette smoking has been shown to decrease the risk of HP [2, 202–204]. Studies have demonstrated that smoking individuals who are exposed to inhaled causative antigens show a lower antibody response [101, 205]. In a survey of 102 pigeon breeders, only 4.3% of smokers presented with elevated IgG antibodies compared to 55.4% in the non-smoking group, although avian exposure was similar [204]. However, in patients with HP, smoking may lead to a more chronic disease and a poorer prognosis [203].

Prevention

Interventions in the work and home environment aimed at limiting exposures to possibly causative antigens occupies a central role in the prevention of HP as the populational risk is largely attributable to environmental exposures. A minority of prospective studies have looked at the efficiency of preventive measures on the incidence of occupational HP (Table 2) [3, 71].

In regard to FLD, the introduction of modern farming practices has led to a decline in the incidence of the disease [122]. The most important preventive measures include the proper drying of hay and cereals before storage, the more extensive use of silage, the increase in ventilation of agricultural yards with continuous flow systems and the introduction of mechanical feeding systems [114, 206]. Drying or heating of the hay before storage has been shown to reduce antigen levels [114, 207]. Furthermore, low-density square bales hinder the growth of microorganisms, although they are being replaced by round bales despite containing higher humidity levels, as they are easier to store and represent a lower labor burden [114, 119].

Among other occupational HP, metalworking fluid HP may be limited through modifications of the industry's working strategies. Preventive measures include the proper enclosing of MWF machinery, elimination of mist cooling, re-engineering to remove recirculation circuits and increasing general dilution ventilation as well as additional worker trainings [89, 208, 209]. The use of molecular-based screening of MWF and the monitoring of spatially clustered distributions of contamination may allow for early detection and prevention of MWF HP [137, 140–142].

Upkeep and maintenance of buildings and equipment are crucial to prevent microorganism contaminations of indoor facilities, which are often due to inappropriate moisture control [210]. Humidity levels should be kept under 60% in living areas. Regular maintenance of humidifiers, air-conditioning, heating and ventilation equipment are of great importance. In addition, vaporizers and humidifiers should be emptied daily and cleaned with hydrogen peroxide or chlorine bleach [210].

Complete eradication of an HP inducing exposure is not always feasible, especially in regard to occupational exposures such as the farming or construction industries. Protective equipment including masks and filters may help limit the inhalation of causative antigens, although evidence on their efficiency remain limited [114, 211]. A study by Gourley et Bradwood on the efficiency of protective masks in farmer's lung disease demonstrated that filters retained particles of 0.8 μm with 98% efficiency [212]. Moreover, Kuzaka suggested that dusk masks in routine dairy farming were effective in preventing FLD [213]. Promising results were also shown in BFL and fungi associated HP where industrial dust respirators could substantially and in most cases completely protect against single environmental exposure [214]. Further studies are needed to confirm the protective nature of dust respirators as the current evidence is divergent [215, 216]. Compliance with protective equipment has been shown to be problematic as these devices are often uncomfortable. When choosing personal protective equipment, tolerability of the device and effectiveness in protecting against the inducing agent are to be considered [114, 213]. Reports have been

made of the use of electrostatic dust filters in central air-conditioning systems to limit the antigenic burden in cases of difficult to eradicate causative antigen [218].

Educational resources for the at-risk workers are an essential component of the preventive HP measures. Occupational health professionals may help identify at-risk workforces and collaborate with communities and employers to educate them on exposures and protective equipment [211]. New occupational HP cases should lead to a workplace assessment. Health surveys of the remaining workers following a newly diagnosed HP case may help identify additional workers affected by HP [71, 217].

Future Directions

Ongoing research to better characterize the different causative antigens and environmental risk factors in the occupational and recreational settings is of extreme importance to allow more accurate diagnosis and adequate treatment, as antigen remediation remains the mainstay treatment of HP. Additional data are required to provide more validated and standardized investigative measures for antigen identification as well as improve our understanding of environmental and pollution related risk in the development and progression of HP. Efforts should continue to be made in ways to maximize clinician's knowledge and recognition of HP and the importance of including it in the differential diagnosis of occupational and environmental related lung disease.

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Lung Cancer in Never Smokers

Jorge Ataucuri-Vargas, Ahmed Hussein, and Humberto K. Choi

Introduction

Lung cancer is the most common cause of cancer-related deaths in the United States and in the world [1, 2].

The major risk factor is cigarette smoking [3]. Across the globe the prevalence of tobacco smoking has declined but it remains high. It is estimated that the global prevalence of smoking was 34% among men and 7% among women in 2019 [4]. In the United States, approximately 14% (34.1 million) of adults were current smokers in 2019 [5]. This suggests that tobacco smoking will continue to be the predominant cause of lung cancer. Eighty to ninety percent of the cases of lung cancer occur in ever smokers [6]. However, increased attention has been given to lung cancer cases among individuals who never smoked and to non-tobacco related risks factors.

Never-smokers are defined as individuals who smoked less than 100 cigarettes in a lifetime [7]. Approximately, 10–20% of the cases of lung cancer occur among never smokers [6]. There is little information available regarding lung cancer in never-smokers and there is much debate whether the incidence of lung cancer in never-smokers is increasing.

Several risk factors have been suggested to explain the occurrence of lung cancer in never-smokers. Non-modifiable risk factors identified include certain genetic susceptibility loci (e.g. 10q25.2, 6q22.2 and 6p21.32) [8]. Modifiable risk factors include exposure to radon, environmental tobacco smoke, indoor pollution, and occupational exposures (e.g. asbestos, chromium) [9]. Certain chronic infections and chronic pulmonary inflammatory diseases have also been suggested [10].

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This chapter's goal is to review how the environment plays a role in lung diseases. There are many environmental exposures suggested to be associated with the occurrence of lung cancer. Lung cancer in never-smokers is a good example of how the environment can interact with the lungs. In this chapter, we will discuss the epidemiology, modifiable non-tobacco risk factors, and different aspects of the clinical presentation and treatment of lung cancer in never-smokers.

Epidemiology

In the United States, the number of new lung cancer cases was estimated to be more than 228,000 with more than 135,000 lung cancer deaths in 2020 [1]. The proportion of new lung cancer cases among never-smokers is estimated to be between 22,800 and 45,600. These numbers demonstrate the high burden of the disease and the concern of its public health impact.

Worldwide, the proportion of lung cancer in never-smokers varies significantly according to the geographic location. While 10–20% of lung cancer patients in Europe and the United States are never-smokers, the proportion in Asia can be as high as 40–50% [11]. The reasons for these differences are not clear, but genetic predisposition and environmental risk factors such as indoor pollution have been suggested as possible causes of geographic variation [11].

This proportion also varies according to gender and ethnicity. It is estimated that 15% of lung cancers in men and up to 53% of lung cancers in women occur in never-smokers [12]. In East and South Asia, female proportion of lung cancer in never-smokers reaches 61% and 83%, respectively [13].

There has been debate whether the incidence of lung cancer in never-smokers is increasing [14]. Pelosof et al. conducted a retrospective study using lung cancer registry data from two hospital systems in Texas and one in Tennessee between 1990 and 2013 [15]. The study identified an increase in the proportion of non-small cell lung cancer (NSCLC) cases among patients who had never smoked. The proportion of never-smokers with NSCLC increased from 8% in the years 1990–1995 to 14.9% in 2011–2013 [15]. These results suggested that the incidence of lung cancer in never-smokers was rising. This was a hospital-based study and the results were not generalizable. Therefore, population-based studies were needed.

Siegel et al. analyzed population-based cancer registries in 7 states (Alaska, Colorado, Florida, Idaho, Louisiana, North Carolina and Rhode Island) from 2011 to 2016 [16]. The proportion of never-smokers was 12.5%. The proportion of never-smokers with lung cancer was higher in women than men, and the most common histology was adenocarcinoma which is consistent with other studies [16, 17]. However, this study did not report whether there was an uptrend of this proportion over time. Hosgood et al. estimated lung cancer mortality from 1992 to 2011 using data from the National Longitudinal Mortality Study and from Tobacco Use Supplements. Among 4900 lung cancer deaths, 13.5% were among never smokers. The authors also reported that the age-adjusted-mortality per 100,000 increased by approximately 20% from the period of 1992–2001 to 2002–2011 (17.5 vs 20.8) [18].

The question whether the incidence of lung cancer in never-smokers is increasing has been attempted to be answered elsewhere. Thun et al. pooled data from 13 large cohort studies and 22 cancer registry studies located in India, China, other selected areas in Asia, Africa, Europe and Middle East [19]. This study did not identify any temporal trends from 1959 to 2004 with the limitation of the study not capturing more recent trends [19].

In summary, it is not clear whether the incidence of lung cancer in never-smokers is truly rising. As population-based data is limited, further research is necessary to estimate the incidence of lung cancer in never-smokers and to determine whether it has been rising over time. Another question that would need to be addressed is "why". Assuming that the incidence is indeed rising, what are the factors that are causing an increase in the incidence in lung cancer in never-smokers? It is imperative for these questions to be addressed considering the burden of the disease. We discuss below some factors that have been suggested to be associated with lung cancer in never-smokers.

Non-tobacco Risk Factors for Lung Cancer

Non-modifiable risk factors include family history of lung cancer and genetic factors. First degree family lung cancer history confers a 1.5-fold higher risk of lung cancer in never-smokers, with an increased risk up to two-fold in African-American ethnicity [20]. Genetic susceptibility loci is an important area of investigation and some have already been suggested (e.g. 10q25.2, 6q22.2 and 6p21.32) [8]. Other candidate genes for this association include *VT11A*, *ROS1*, *DCBLD1*, and HLA Class II region [8]. In a recent large genome-wide association study using a European-descent cohort, 3 different single nucleotide polymorphism were found in chromosome 5 which coded for telomerase enzyme. Genetic variations in this location are associated with other cancers such as lung cancer in smokers, breast, ovarian, colorectal, and prostate cancer [21].

Many non-tobacco related agents, exposures and activities associated with lung cancer have been identified. The International Agency for Research on Cancer (IARC) has developed a list of lung carcinogens [9]. An agent or occupation process is classified as category 1 when there is enough evidence of association with lung cancer. Probable carcinogenic agents to humans are classified as Group 2A, possible agents as Group 2B, not classifiable as Group 3 and probably not carcinogenic to humans as Group 4. It is challenging to determine whether a specific agent is the cause of lung cancer. Biologic plausibility and population-based studies are necessary to establish a causal relationship between a specific exposure and lung cancer. Causal inference can be reached if epidemiologic studies show consistency, strength of association, specificity, temporality, coherence, plausibility and analogy, dose-gradient response and experimental support [22]. These necessary components have been demonstrated with tobacco smoking and lung cancer, however this is not always the case among non-tobacco exposures. It is challenging to detect and measure the intensity of exposure to specific agents, and longitudinal, prospective

studies are not practical. Most of the studies supporting the association of non-tobacco agents and lung cancer are based on observational case-control or cohort studies. These types of observational population-based studies are susceptible to multiple biases such as confounding, reverse association, selection bias, exposure measurement error and recall bias [23]. For example, epidemiologic studies in air pollution have been cited to suffer from different forms of confounding and exposure measurement error [24].

We discuss below some non-tobacco agents or exposures that have been associated with lung cancer: radon, environmental tobacco smoke, occupational exposures, indoor pollution, lung infections and chronic lung diseases. We also review the evidence regarding "vaping" as this is a newer exposure of concern.

Radon

Radon is a naturally occurring radioactive gas. It is a decay product of uranium-238 and thorium-232 (Fig. 1). It is primarily formed in soil but it can also be found in surface water, metal mines (e.g. uranium, phosphorus, silver, gold), in coal combustion residues, and in natural gas. It tends to concentrate in poorly ventilated areas where the geological substrate is rich in Uranium-238 content [25].

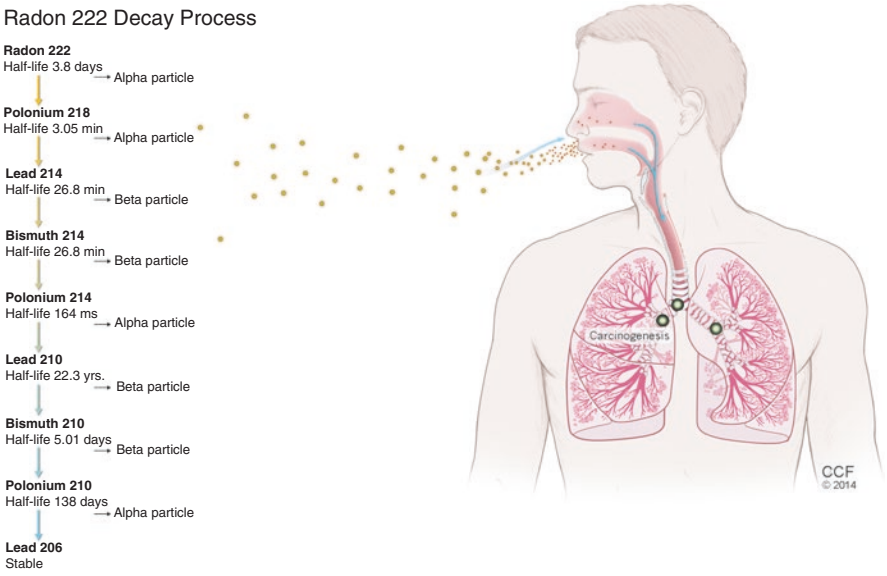

Fig. 1 Natural decay and trajectory of radon-222 into the airways [129]. (Reprinted with permission from: Choi and Mazzone [129]. Copyright © 2014 Cleveland Clinic Foundation. All rights reserved)

Radon is considered to be the second most common lung cancer risk factor after cigarette smoking. Residential radon exposure is considered to be the leading cause of lung cancer in never smokers [26]. It is estimated that up to 21,000 people die annually of lung cancer due to radon in the United States [27]. The evidence of association between radon and lung cancer comes from large cohort studies involving underground miners [28]. Several studies have reported association between residential radon with lung cancer in the general population, however it is important to note that they extrapolate the data and knowledge obtained from the prior cohorts involving miners [29].

Radon is a colorless, odorless, tasteless, and chemically inert radioactive gas which emits alpha particles travelling attached to dust or as free particles to the airway by inhalation route. The radon daughters or progenies, polonium-218 and polonium-214, emit alpha particles that are highly effective in damaging tissues. After deposition on the mucosal surface the radioactive emissions destroy and damage mucosal cells increasing the risk of cancer by several mechanisms including gene mutations, chromosome aberrations, generation of reactive oxygen species, up or down-regulation of cytokines, and production of proteins associated with cell-cycle regulation [30].

Radon shows a linear dose-response relationship without an specific threshold for being associated with lung cancer [31]. There is no safe radon level. A radon level of 4 Picocuries per liter (pCi/L) or 200 Becquerel per cubic meter [Bq/m3]) is the concentration at which mitigation actions are suggested [32]. Due to its higher density compared to air radon tends to concentrate in lower levels (basements, ground floors) [33]. The United States Environmental Protection Agency recommends that all homes be tested for indoor radon levels [32].

There is no specific or predominant lung cancer histology associated with radon. All histologic subtypes have been described in association with radon [34]. In addition, there is no specific histopathologic or molecular feature to attribute an individual case of lung cancer to radon exposure. Therefore, it is not possible to link radon exposure to one individual case of lung cancer using our current clinical tools.

Environmental Tobacco Smoke

Secondhand smoke or environmental tobacco smoke (ETS) refers to involuntary inhalation of smoke by nonsmokers. It is a mixture of exhaled mainstream smoke produced by the active smoker with side stream smoke, which is produced by the smoldering cigarette, cigar or pipe [35].

Microenvironments are determinants of ETS burden exposure to individuals. For adults, social and workplace microenvironments are the predominant locations of exposure, whereas for children, the home microenvironment is the predominant exposure location. Mitigation and control strategies are based on microenvironments [36]. There has been an improvement on the success of ETS exposure mitigation and control strategies in the recent years. In the United States, ETS exposure

among non-smokers has decreased from 88% in 1988 to 25% in 2014. Unfortunately, the decrease was stagnant during 2011–2012 and 2013–2014. ETS exposure prevalence was highest among non-smokers aged 3–11 years, non-Hispanic blacks and those who were living in poverty, in rental housing, or with someone who smoked inside the home [37].

ETS is associated with more than 1.2 million premature deaths worldwide every year, primarily from cardiovascular and respiratory diseases, including lung cancer [38]. Since Hirayama et al. published in 1981 the association of ETS and lung cancer several studies have confirmed the results [39, 40]. In a pool analysis of 18 case-control studies including never-smokers, those exposed to ETS had an odds ratio of 1.31 for lung cancer, and the histological type of small cell lung cancer had the strongest association with ETS [41].

There is no safe level of ETS exposure and it can lead to changes in the airway epithelium even at low levels [42]. The exact carcinogenic mechanism of ETS still needs to be fully elucidated. Sidestream smoke contains higher concentrations of ammonia, nitric oxides, and carcinogens compared to mainstream smoke [43]. Mechanisms that have been suggested include the recruitment of inflammatory cells to the lung (neutrophils and macrophages), oxidative damage, and direct binding to DNA to affect the expression of genes related to chronic inflammation [44]. The main link between chronic inflammation and oncogenesis is considered to be TNF-α mediated upregulation of NF-κB (Nuclear factor-κB), which induces anti-apoptotic and proliferative effects [44].

Tobacco smoke can deposit in nearby surfaces. A new-coined term, third-hand smoke refers to smoke components deposited on surfaces (e.g. walls, doors, drapery, carpets, clothes, furniture, flooring material) along with metabolites of these components generated through oxidative chemistry. It is not clear whether third-hand smoke is associated with increased risk of lung cancer [45].

Occupational Exposures

Lung cancer is the predominant type of occupation-related cancer, representing up to 86% of all occupation-related cancers [46–48]. Several specific agents, exposures and certain activities have been associated with lung cancer (Table 1) [9]. The mechanisms of carcinogenesis may vary according to the agent and exposure. Some mechanisms that have been suggested include oxidative stress-mediated DNA damage, chronic inflammation and epigenetic changes [49, 50].

A large study analyzed the global and regional burden of cancer due to occupational carcinogens categorized as Group 1 by IARC [46]. It was estimated that occupational exposure to carcinogens led to 349,000 deaths and 7.2 million disability-adjusted life years worldwide in 2016 [46]. Men were predominantly affected (79%). In high-income countries, the main carcinogen associated with increased risk of death was asbestos followed by environmental tobacco smoke,

Table 1 Occupational agents, exposures and settings recognized as human carcinogens [9, 130, 131]

Exposures	Examples of occupations or settings
Arsenic	Nonferrous and copper mining; electronic semiconductor production; wood preservation; production or application of pesticides; "sheep dip" liquid manufacturing.
Asbestos	Asbestos miners and millers; asbestos-containing products manufacturing (e.g. textiles and insulation products); construction (e.g. insulators, boiler makers); shipyards.
Beryllium	Aerospace, defense, automotive, and electronic industries.
Bis (Chloromethyl) Ether and Chloromethyl Methyl Ether	Manufacture of plastics, polymers, S-2 containing mosquito coils, and ion exchange resins.
Cadmium	Production, refining, and processing of cadmium and its alloys; manufacture of batteries, and pigments; alloy production and plating.
Chromium (VI)	Steel, refractory brick production and electroplating, Chromium (VI) in chromate production, chrome electroplating and plating, chromium-containing paints and pigments; welding or cutting/grinding of chromium-containing metals and alloys; leather tanning; glass manufacturing.
Coal dust, biomass fuel	Indoor cooking with coal or biomass fuel
Coal-tar pitch	Road pavers, roofers, asphalt workers.
Diesel engine emissions	Underground mining and construction; vehicle drivers (e.g. truck drivers) and mechanics; airline personnel; railroad workers; ship and dock workers; toll booth attendants; bridge and tunnel workers; garage workers; farm workers; heavy equipment operators; firefighters.
Haematite	Iron mining
Nickel	Nickel mining, refining and smelting; alloy and stainless steel manufacture; nickel electroplating; production of ceramics, magnets, batteries, paint, stainless steel, nickel-containing dyes/pigments textiles, carnish and vacuum tubes.
Outdoor air pollution (particulate matter)	Police, drivers, street vendors.
Radiation	Radon: Uranium miners; nuclear waste repositories; natural caves; phosphate fertilizer plant; oil refinery; utility tunnel; subway tunnel; construction excavators; power plant workers; radon "health" mines; radon balneotherapy spas; water plant operators; fish hatchery attendants. Plutonium: Nuclear fuel and weapon production facilities; plutonium production workers. Gamma-radiation, X-radiation: Aviation and space workers; gas and oil extraction; industrial radiography; mining and milling, nuclear power facilities, nuclear weapons production and research.
Second-hand smoking	Home, restaurants, bars, casinos, planes.
Silica dust, crystalline	Silica ceramics production; diatomaceous earth; ore mining; quarries; sand and gravel operations
Soot	Chimney sweeps; firefighters; building demolition personnel; brick masons and helpers; heating/ventilation and air conditioning worker; metallurgical workers and insulators.

(continued)

Table 1 (continued)

Sulfur mustard	Storage and destruction of mustard gas-containing soil/containers; construction workers, laboratory workers, fishing, warfare.
Other exposure or activities[a]	Aluminum production
	Acheson process manufacturing (synthesis of graphite and silicon carbide (SiC) used as an abrasive)
	Coal gasification
	Coke production (e.g. coal coke oven emission)
	Iron and steel founding
	Rubber manufacturing industry
	Painting
	Welding

[a] No specific discrete carcinogenic agent identified but there is evidence to consider the occupation or activity as high risk according to International Agency for Research on Cancer

silica and diesel exhaust [46]. Notably, from 1990 to 2016 a downtrend in occupation-related cancer mortality was noted [46].

Rushton et al. estimated the burden of cancer deaths attributable to occupational factors in Great Britain in 2004 [51]. Asbestos contributed over half the occupational attributable deaths, followed by silica, diesel engine exhaust, and radon. Among all occupations, construction workers deaths due to occupational exposure represent about half of cases, with lung cancer being the cause in 47% of deaths. Other occupations with high number of deaths included metal working, personal and household services, mining, land transport and services allied to transport, roofing, road repair/construction, printing, farming, military personnel, some other service industry sectors and manufacture of transport equipment, fabricated metal products, machinery, non-ferrous metals and metal products, and chemicals [51].

It is important to note that the majority of participants in occupational exposure studies are men and tobacco smokers. Women and never-smokers are included at a much lower proportion. Tobacco smoking is an important confounder when analyzing occupation exposures and it might become a residual confounder despite statistical adjustment [52–54]. Furthermore, co-exposure of certain occupational exposure with tobacco smoking leads to additive synergism for lung cancer [55]. Ngamwong et al. conducted a meta-analysis including 17 case-control and cohort studies to estimate the risk of lung cancer associated with asbestos exposure and cigarette smoking. The study showed a significant difference in the risk of developing lung cancer in subjects exposed to asbestos and history of smoking compared to those exposed either to asbestos or smoking separately or none [55]. The odds ratio for lung cancer was 1.7 among those exposed to asbestos and non-smokers, 5.6 for smokers and no asbestos exposed, and 8.7 for those exposed to both asbestos and smoking [55].

As old exposures become less common or disappear (e.g. chrysotile asbestos has been banned in the European Union since 1991), new emerging exposures require investigation. For example, carbon nanotubes, nanotechnology material (e.g. Mitsui MWCNT-7), and indium-tin oxide, used in flat-panel displays (e.g. plasma screen for television), were recently classified as possibly carcinogenic to humans (IARC

Group 2A) [56, 57]. There are also old-known carcinogens reemerging. Workers sandblasting jeans to give denim a 'worn look' have high exposure to silica causing outbreaks of silicosis [58].

Indoor Air Pollution

A third of the world's population, predominantly in low and middle-income countries, use solid fuel (biomass or coal) for cooking, heating or lighting [59]. Indoor air pollution contains carbon (particulate fraction of smoke), carbon monoxide, polycyclic aromatic hydrocarbons, aldehydes and free radicals among other toxic inorganic and organic compounds [60]. It is estimated that solid fuel emissions account for 17% of all lung cancer deaths in men and 22% in women in low and middle-income countries [61]. Coal smoke is considered a Group 1 carcinogen. Other solid fuels smokes (e.g. wood) are classified as probable carcinogens (IARC Group 2A). Several studies linking coal smoke and lung cancer have been reported [62]. The evidence linking wood smoke and lung cancer is weaker [63]. There is not enough evidence to suggest that other solid fuels such as animal dung, domestic rubbish, and plant residues are associated with lung cancer [60].

Infections

Tuberculosis

Tuberculosis (TB) remains an important cause of morbidity and mortality worldwide [64]. There is evidence that suggests that pre-existing pulmonary tuberculosis is an independent risk factor associated with increased risk of developing lung cancer [65].

One meta-analysis including 30 studies examined the relationship between lung cancer and tuberculosis while adjusting for smoking. The observed effect across the identified studies suggested that the relative risk of lung cancer for individuals with a previous history of tuberculosis was 1.76 [66]. The pathophysiology of tuberculosis as a risk factor for lung cancer has not been fully elucidated [67]. One hypothesis would be that inflammation associated with infections can contribute to carcinogenesis in patients with chronic pulmonary tuberculosis. In addition, metaplastic and proliferative changes which tuberculosis leaves behind in the bronchial and alveolar mucosa can be a possible place later for malignant transformation [64].

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) infection remains an important global health issue with millions of people affected [68]. In HIV-infected individuals, lung cancer is a leading non-acquired immunodeficiency syndrome (AIDS) defining cancer and

is the most frequent cause of cancer deaths [69]. Even after controlling for smoking, HIV infection is an independent risk factor for developing lung cancer [70].

HIV could promote lung cancer through multiple mechanisms. Transactivator of transcription (*Tat*), a gene involved in HIV-1 replication, by down-regulation of the tumor suppressor gene *p53*, increases expression of proto-oncogenes [71]. A study by Tong et al. suggesting an association between the down-regulation of *TIP30* (a putative tumor-suppressor gene located on human chromosome 11p15.1) and promotion of metastatic progression of lung cancer [72]. Inflammation has been investigated in individuals with HIV as a contributor to the increased lung cancer risk. Also, other associated infections in these patients have been proposed as a source for the acute inflammatory insult that potentially contributes to the development of lung cancer [69].

Human Papillomavirus

Human papillomavirus (HPV) is a double-stranded circular DNA virus that commonly infects humans. The risk of being infected at least once in a lifetime among both men and women is 50% worldwide [73]. It is considered as one of the most important human oncogenic viruses, and has been shown to be associated with numerous malignancies including breast, cervical, oropharyngeal and prostate cancer [74].

The oncogenic characteristics of HPV derive from the oncoproteins *E6* and *E7*, sections in HPV genome, that interact with *p53* and retinoblastoma (*RB*) tumor suppressors which lead to enhanced cell proliferation, resistance to apoptosis and chromosomal instability [74, 75]. HPV has also been considered a risk factor for lung cancer. Several studies have shown the presence of HPV DNA and HPV *E6-E7* in lung cancer cells [71]. Hussen et al. studied tissues from 109 lung cancer cases and reported that HPV genome was detected in 51.4% of lung cancer tissues with a significant association between the presence of HPV and lung cancer [76]. In a Brazilian cohort of patients with lung cancer, HPV was found to be present in 33 of 63 lung cancer pathology samples. Most of the cases where HPV was detected were squamous cell carcinomas. But it was also detected in other histologic subtypes including adenocarcinoma, small cell carcinoma and large cell carcinoma. The *E6* and *E7* oncoproteins were detected by immunohistochemical stain technique in 28 and 25 out of 33 samples, respectively [77].

Helicobacter Pylori

Helicobacter pylori (*H. pylori)* is a common bacterial pathogen that affects more than half of the population worldwide and it is responsible for substantial gastrointestinal morbidity [78]. Growing body of evidence has supported the association of *H. pylori* infection with extra-digestive diseases including lung cancer [79].

One meta-analysis including 7 observational studies reporting data on 16,244 lung cancer cases and 1707 patients with seropositivity for *H. pylori*. The study found that *H. pylori* infection was associated with significantly increased risk of lung cancer with a pooled odds ratio of 2.29 [80]. The inflammatory and immune responses triggered by *H. pylori* infection are proposed as the main mechanisms associated with the extra-digestive pathologies and carcinogenesis [79, 81].

Chronic Lung Diseases

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterized by progressive fibrosis of the lungs that causes irreversible loss of pulmonary function [82, 83]. IPF is a risk factor for developing lung cancer, with a risk nearly five times as high as that of the general population [84, 85]. There are similarities between IPF and lung cancer in genetic features. Both diseases share features of increased proliferation, dysregulation of specific signaling pathways and abnormal expression of microRNAs [86, 87].

The lung cancer prevalence in patients with IPF ranges from 2.7% to 31.3% which increases with each year following IPF diagnosis as cumulative incidence at 10 years of follow up exceeds 50% [84]. This suggests that the incidence of lung cancer may be affected by the use of anti-fibrotic treatment and prolonging survival of patients with IPF. The risk is higher with male sex, older age, history of smoking, and coexisting emphysema [84, 88]. Many studies showed that patients with IPF developed lung cancer more frequently in the peripheral areas of lower lobes, where fibrosis is predominant, and squamous cell carcinoma and adenocarcinoma are the most common histologic subtypes (Fig. 2) [86, 89].

Surgical resection, chemotherapy and radiation therapy or combinations of these regimens represent the therapeutic modalities used, similar to the management of lung cancer in the general population. In early stages surgical resection is effective but associated with high risk of postoperative complications and the impact on postoperative lung function is a major concern. There is no consensus regarding the best strategy for patients who are considered inoperable. Data regarding chemotherapy and radiation therapy effectiveness are limited [89]. Lung cancer significantly affects the survival of patients with IPF. The mean survival time is reduced by 1.6–1.7 years compared to patients with only IPF [88].

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) has been suggested as a risk factor for lung cancer [90]. COPD and lung cancer share common features. The main one is the common risk factor of smoking. Although this chapter discusses non-tobacco

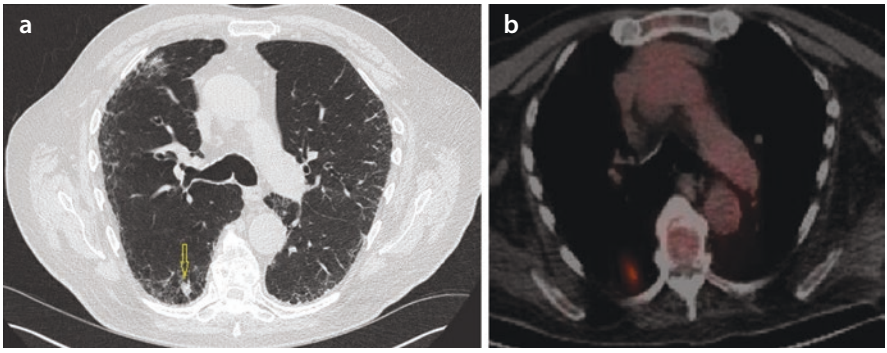

Fig. 2 (**a**) CT chest showing areas of abnormal reticular disease, architectural distortion and traction bronchiectasis with a basilar, peripheral predominance. Solid nodule in the right lower lobe superior segment measures approximately 7 × 12 mm (arrow). (**b**) PET scan showing that the right lower lobe nodule is hypermetabolic. Pathology from wedge resection revealed adenocarcinoma

related risk factors for lung cancer, it is relevant to discuss the role of COPD and lung cancer. The nature of the link between COPD and lung cancer remains obscure but several mechanisms have been suggested [91]. COPD may be a driving factor in lung cancer by increased cellular proliferation, chronic exposure to pro-inflammatory cytokines, increasing oxidative stress and the resulting DNA damage and repression of both DNA repair mechanisms and innate immunity [92].

Several studies have demonstrated that COPD is associated with increased risk of developing lung cancer independent of smoking exposure [93]. In a systematic review that included 11 studies, 28.4–39.8% of patients with lung cancer had a diagnosis of COPD and 47–76% had emphysema [93]. One meta-analysis of thirty-nine studies demonstrated that a previous history of COPD, chronic bronchitis or emphysema conferred a combined relative risk of 1.80 of developing lung cancer [66]. It is important to underscore that there might a residual confounding from tobacco that explains the effect of COPD, chronic bronchitis or emphysema among smokers. They did not observe a significant association between COPD, emphysema and chronic bronchitis with lung cancer among never smokers in this study.

Sarcoidosis

Sarcoidosis is a chronic multisystem inflammatory disease characterized by development of non-caseating granulomas. The lungs are most commonly affected, but nearly any organ in the body can be involved [94]. The possible link between sarcoidosis and lung cancer is controversial. Chronic inflammation, immune dysfunction, and genetic susceptibility to both cancer and autoimmune diseases are among several mechanisms that have been suggested to explain the relationship between sarcoidosis and cancer [95]. In a meta-analysis including 16 studies and over 25,000 patients, the relative risk for development of invasive cancers was 1.19. The selected sites with a significant increased risk included skin, hematopoietic, upper digestive,

kidney, liver and colorectal cancers. The authors did not find a significant increased risk specifically for lung cancer. It is important to note that there was a high degree of heterogeneity among the included studies [95]. Additional research is necessary.

Electronic Cigarettes

Electronic cigarettes (e-cigarettes) or vapes are battery-powered devices designed to deliver nicotine or other substances by heating a liquid that emits an aerosol [96, 97]. It is estimated that e-cigarettes are used by 6.9 million adults in the Unites States. Rates of e-cigarette use are higher in young people and have accelerated recently [97–99]. Adolescent e-cigarette usage is a major public health concern, with 1 in 6 high school students reporting current e-cigarette use [100].

E-cigarette use is now widely recognized as a potential cause of lung injury after an outbreak of severe cases of acute lung injury and acute respiratory distress syndrome that led to thousands of hospitalizations and dozens of deaths in 2019 [101]. It is not clear what all the factors that led to the outbreak were. Liquids containing vitamin E acetate has been suggested as possible cause [102].

There is evidence suggesting e-cigarettes have the potential to be carcinogenic. E-cigarettes can emit volatile carbonyls, reactive oxygen species, furans, and metals (nickel, lead, chromium) many of which are toxic to the lungs [103]. There are in-vitro, animal and transcriptome studies showing deleterious effects. An in-vitro study using immortalized human bronchial epithelial cells found similar gene expression in exposure to electronic cigarette-conditioned media compared to tobacco-cigarette conditioned media [104]. An animal study assessing e-cigarette aerosol exposure in mice reported higher rates of lung adenocarcinoma and bladder urothelial hyperplasia exposed to e-cigarette aerosol compared to mice exposed to vehicle control or filtered air [105]. In a transcriptome analysis study comparing e-cigarette users, smokers and non-smokers, gene expression was explored in oral mucosa cells. E-cigarette users as well as combustible cigarette smokers were found to have higher rate of deregulated cancer-related pathways compared to controls [106].

These devices may contain nicotine which is highly addictive, and they are widely popular among teenagers and young adults. This raises the concern that prolonged exposure to e-cigarettes could be a new risk factor for lung cancer at a proportion to be a public health issue in the future. Large, longitudinal and prospective studies are urgently needed.

Clinical Presentation of Non-tobacco Related Lung Cancer

Indeterminate lung nodules are a common clinical problem. They trigger the evaluation to estimate the probability of malignancy which can be done by clinical experience or by using validated prediction models [107]. Prediction models need to be

applied with caution in individuals who never-smoked as the models were derived mostly from populations with individuals with history of smoking. Most indeterminate nodules are likely benign but a malignant nodule is at risk of being underestimated in someone with no history of smoking when a prediction model is used. Some known non-tobacco risk factors for lung cancer may be present in the clinical history. For example, an individual who had exposure to asbestos by working at shipyards for many years. However, there are currently no validated models that can be used in clinical practice to estimate the risk of lung cancer of a nodule that incorporate non-tobacco risk factors such as environmental or occupational exposures.

There is often misdiagnosis or delayed diagnosis of lung cancer in never smokers. The fact that most individuals are asymptomatic at the time of diagnosis likely contributes to the delay in diagnosis and most cases are found at advanced stages [108, 109]. Abnormalities on chest imaging may also be misdiagnosed as lung infections and cause delay in the diagnosis and treatment of lung cancer [110]. In a French cohort, 73% of lung cancer cases in never-smokers were diagnosed at stage IV [111]. In another cohort, stage IV lung cancer was diagnosed in 62% of never smokers compared to 49% in ever smokers [108].

A predictable question that may be raised by never-smokers who are diagnosed with lung cancer is what could have caused the disease. There are no specific tests that help determine whether a specific agent, exposure or activity is the main risk factor that led to lung cancer in an individual. Clinicians rely mostly on a thorough history and physical examination, and imaging findings. Some clues might arise during the diagnostic evaluation. For example, the presence of pleural plaques suggest exposure to asbestos, and the detection of HPV in the biopsy or resection specimens suggests that the virus might have played a role.

Subsolid (ground glass and part-solid) nodules that persist on surveillance scans are suspicious for a lesion in the spectrum of adenocarcinomas [112]. This is a common presentation among never-smokers especially in Asia [113]. It is important to note that adenocarcinomas and other histologic subtypes may present with other radiographic patterns [114]. As discussed above, most patients are diagnosed at advanced stages. Therefore, findings suggestive of metastatic disease such as adenopathy, pleural effusion, pericardial effusion, brain lesions may be present and require diagnostic evaluation.

Overall, NSCLC is the most common type in smokers and never-smokers. The predominant subtype in never-smokers is adenocarcinoma [108, 111]. Most non-tobacco risk factors have been associated with NSCLC except for environmental tobacco smoke which has been more strongly associated with small cell lung cancer [41].

Certain molecular markers are more frequently found among never-smokers compared to ever-smokers. This highlights the importance of molecular characterization in never-smokers in view of the role and increasing number targeted therapies available. Mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase are found in 42.5% in never smokers compared to 5% in smokers [115]. The incidence of *EGFR* mutations can be as high as 60–78% in East Asian cohorts [116]. Chromosomal rearrangement involving the receptor tyrosine kinase receptor (*ALK/ROS1/RET*) is overall found in 5% of NSCLC tumors [117]. The *ALK*

alteration is more common in younger patients, with history of light smoking or never-smoking [118]. In a database of patients with *ALK* alteration, never smokers comprised 70% of the cases [118]. In contrast, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations and programmed death-ligand 1 (PD-L1) high expression levels are more common among smokers [119, 120].

The prognosis of lung cancer depends on multiple factors including the stage of the disease, histologic subtype, presence of molecular markers as well as the presence of comorbidities and performance status. Important comorbidities include tobacco-related chronic lung and cardiovascular diseases among smokers. The impact of non-smoking on the prognosis of lung cancer in never-smokers is not clear. Several cohorts have demonstrated conflicting results and it is uncertain whether the overall the prognosis of lung cancer in never-smokers is different compared to ever-smokers [121, 122].

Screening

Lung cancer screening with low-dose CT scan is now standard of care [123]. The eligibility criteria is based on age and history of smoking: age of 55–74 years, a history of smoking of at least 30 pack-years, and either current smokers or former smokers who had quit within the past 15 years [123]. An update of the eligibility criteria is currently being proposed based on the recent results of a large, randomized control trial [124]. Some professional societies expand on this criteria to include additional risk factors for lung cancer such as radon, environmental tobacco smoke and occupational exposures (e.g. asbestos) [125]. However, the inclusion of such exposures to the eligibility criteria for screening has not been tested in randomized trials, and the balance of benefit and potential risks is uncertain. Another approach to identify patients for screening that has been proposed is the use of prediction models that estimate the risk of developing or dying from lung cancer, or their potential to benefit in life-years gained [126, 127, 128].

Lung cancer screening in never-smokers is not recommended based current eligibility criteria. The role of screening in never-smokers has been far less studied. The field is in need of better tools to help quantify non-tobacco risk factors, better understand the interaction of genetic susceptibility with the environment, estimate the risk of developing lung cancer, and potentially identify individuals who would benefit from screening.

Conclusion

Lung cancer in never-smokers is a good example of how the environmental factors can increase the risk of developing lung disease. Most cases of lung cancer are associated with tobacco smoking. Although in a smaller proportion, lung cancer in never-smokers is an important public health concern. Many non-tobacco risk factors

have been suggested. However, it is not clear how much each non-tobacco risk factor contributes to the burden of the disease at a population level or for an individual. Although the initial clinical evaluation is similar, the clinical features of lung cancer in never-smokers are distinct from the disease in ever-smokers and they impact the treatment options. This is an area with vast opportunities for additional research to continue to understand who the susceptible individuals are, how the environment affects their risk of developing disease, and how to best identify them and treat them.

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Acute and Chronic Lung Disease from Recreational Inhalants

Anne E. Reihman, Fernando Holguin, and Sunita Sharma

Introduction

The lungs are one of the key barriers for preventing harmful substances from entering the body. Under normal physiologic conditions, the nasal passages filter out dust, pollutants, and pathogens from inspired air, whereas the lower airways clear smaller particles via a combination of mucociliary clearance and the response of innate immune cells that reside in the lung parenchyma. In the setting of high concentrations of inhaled agents, such as tobacco smoke, these protective mechanisms become overwhelmed leading to pulmonary airway and parenchymal damage.

This chapter will focus on recreational inhalants and their impact on the lung. Specifically, the acute and chronic effects of electronic (e-)cigarettes, vaping, hookah, marijuana, and other inhaled illicit and commercial agents will be discussed. The epidemiology of use, proposed mechanism of injury to the lung, and what is currently known about the acute and chronic pulmonary complications of each will be reviewed.

Electronic (e-)Cigarettes and Vaping

E-cigarettes, also known as electronic nicotine delivery systems (ENDS), are handheld devices that include a nicotine-containing aerosol, which is inhaled delivering nicotine without tobacco smoke. Since first appearing on the market around 2007, they have evolved from devices resembling cigarettes ("cigalike") to variable shape

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and size electronic devices that are largely unregulated in terms of their manufacturing specifications [1, 2].

E-cigarettes consist of a cartridge containing nicotine, a solvent such as vegetable glycerin or propylene glycol, and often one or more of 7000+ available flavorings [1]. The liquid is heated and then rapidly cooled to produce an aerosol that is inhaled or "vaped" by the user through a mouthpiece [3]. Although there is the option to omit nicotine from certain brands of e-cigarettes, the majority contain some amount of nicotine in variable levels. A 2014 systematic review found nicotine levels in e-cigarette liquids ranged from 0 mg/ml to 87.2 mg/ml. However, it was also noted that the nicotine content listed on e-cigarette solutions often significantly differed from the measured values. Further, nicotine delivery could vary between different e-cigarette devices within the same brand as well as from puff to puff using the same device [4]. Studies have shown the variable nicotine content in e-cigarettes can result in higher exposure to nicotine than from conventional cigarettes [5] potentially increasing their addictive potential.

E-cigarettes were initially intended to be used as assistive devices for smoking cessation. More recently, they have gained popularity as recreational devices especially among adolescents and young adults, many of whom have never smoked conventional cigarettes [6]. In 2018, 14.9% of adults in the United States reported having ever used an e-cigarette. Of those, 8.1 million (3.2%) reported being current e-cigarette users with the highest use in the 18–24-year-old age group [7]. From the most recent estimates of use released by the Centers for Disease Control (CDC) in 2020, 19.6% (3.02 million) high school students reported current e-cigarette use with 22.5% of those reporting daily use. Further 4.7% (550,000) middle school students reported current cigarette use [8]. The use of e-cigarettes in adolescence has been shown to be associated with increased likelihood of future use of combustible tobacco products [9] and cannabis [10], raising concerns about the long-term public health effects of e-cigarette use.

Despite the initial perception that e-cigarettes would be a safer alternative to conventional combustible tobacco products, it is now clear that e-cigarette use is not without consequence. However, given their relatively recent rise in popularity, the long-term impact of e-cigarettes on users' health remains to be determined. Additionally, significant heterogeneity between devices and their liquid components complicates research on the comparative safety of e-cigarette products [3]. The sections below discuss what is currently known about the acute and chronic effects of e-cigarettes on the lung including a review of the recently recognized clinical syndrome of e-cigarette or vaping product use-associated lung injury (EVALI).

Acute Pulmonary Complications of e-Cigarettes

From in vitro and in vivo studies, it has been shown that e-cigarettes create an acute inflammatory response and increase oxidative stress in the lungs [3, 11]. While clinical data remains limited, these biological mechanisms are likely the etiology for the patterns of observed acute lung injury discussed below.

Since the first case of e-cigarette-associated lung injury was published in 2012 [12], there has been growing evidence that vaping can cause acute parenchymal lung injury. The most well-known pattern of this acute lung injury is EVALI, but additional patterns of parenchymal lung injury have also been described. In 2020, Tzortzi and colleagues published a systematic literature review of currently published e-cigarette-related clinical cases. Of the 238 individual cases identified, 24% were respiratory cases. The most common diagnosis was EVALI (26%) followed by organizing pneumonia/bronchiolitis obliterans with organizing pneumonia (BOOP)/respiratory bronchiolitis (21%) and lipoid pneumonia (16%). There were additional case reports of e-cigarette-associated eosinophilic pneumonia, hypersensitivity pneumonitis, diffuse alveolar hemorrhage, and acute respiratory distress syndrome (ARDS) [13].

Beyond direct injury to the lung, vaping can also alter respiratory system mechanics adversely impacting the lungs. For example, vaping has been associated with the development of spontaneous pneumothorax [14–16]. The mechanism of lung injury leading to spontaneous pneumothorax is hypothesized to be from deep inhalation through a highly resistive device, such as an e-cigarette, generating a vaping-related Müller maneuver and resultant large negative intrathoracic pressure [14]. This large swing in transpulmonary pressure may predispose to the development of spontaneous pneumothorax, similarly to what is described in marijuana smokers [17]. Other proposed mechanisms include vaping-associated inflammatory injury to the lung parenchyma with resultant bleb formation and rupture causing pneumothorax [16].

Of growing concern during the global pandemic of severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*, also known as COVID-19) is the impact of e-cigarette exposure on the risk of the COVID-19 disease. SARS-CoV-2, the pandemic's causal agent, is a respiratory virus that binds to the angiotensin-converting enzyme 2 (ACE2) receptors in the respiratory tract. The resulting spectrum of respiratory illness can range from being asymptomatic (but infectious) to severe and fatal acute respiratory failure from ARDS. In addition to its impact on respiratory symptoms and the development of respiratory disease, habitual use of e-cigarettes has also been shown to increase the risk of the development of respiratory infections. Notably, e-cigarette use has been shown to increase the risk of *SARS-CoV-2*, infection in both youth and adults [18, 19]. Furthermore, the use of e-cigarettes has been associated with increased mortality related to COVID-19 disease even in adolescent populations [19]. Although the smoking-induced upregulation of the ACE2 receptor identified in cigarette smokers is postulated to be one of the mechanisms underlying the association between vaping and increased *SARS-CoV-2* risk [20], additional research is needed in vaping subjects.

EVALI

As noted above, EVALI is currently recognized as the most common acute parenchymal lung injury associated with vaping and e-cigarette use. EVALI came to the forefront of the public's attention in the fall of 2019 after a cluster of US

hospitalizations for a nonspecific pneumonitis, largely in young adults, was found to be linked to tetrahydrocannabinol (THC)-containing e-cigarette products [21]. The etiologic link between EVALI and vaping product use was ultimately considered to be vitamin E acetate [21, 22]. With exclusion of this additive from vaping products, increased public awareness about the potential harms of THC-containing e-cigarettes, and increased restrictions on the sale of vaping products, the incidence of EVALI cases quickly declined and has remained low [21].

The clinical presentation of EVALI is nonspecific and may include subjective report of several days to weeks of gradual onset cough, shortness of breath, chest pain, fatigue, fever, and/or gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea). Vital sign abnormalities may include hypoxemia, tachypnea, tachycardia, and fever. Laboratory values often show a leukocytosis with neutrophil predominance and elevation of serum inflammatory markers including erythrocyte sedimentation rate *and* C-reactive protein. Liver function tests can also be elevated. Imaging often shows bilateral opacities on chest X-ray or ground glass opacities with subpleural sparing on chest CT. Bronchoscopy with bronchoalveolar lavage may be notable for the presence of lipid-laden macrophages [23–27] (Fig. 1). The majority of EVALI cases have imaging and pathologic patterns consistent with diffuse alveolar damage and/or organizing pneumonia, though acute eosinophilic pneumonia and diffuse alveolar hemorrhage have also been seen [28]. In order to determine a case of EVALI, the CDC recommends the patient meet the criteria outlined in Table 1 [29].

Recommended treatment typically includes supportive care, supplemental oxygen or ventilatory support as indicated, and systemic corticosteroids for severe cases

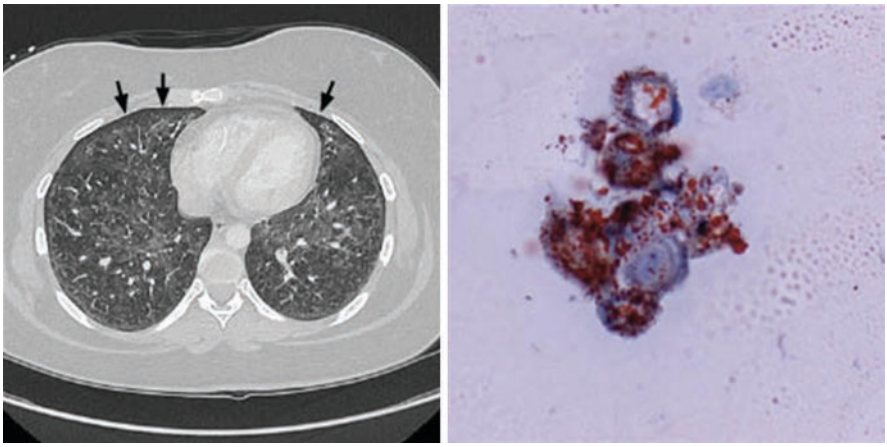

Fig. 1 Representative imaging and cytopathology from a patient with EVALI who reported a history of vaping marijuana. Left panel: CT chest shows the presence of scattered bilateral ground glass opacities with areas of subpleural sparing (arrows). Right panel: Oil Red O stain performed on a cytospin of bronchoalveolar lavage fluid shows lipid droplets within the cytoplasm of nucleated inflammatory cells

Table 1 The 2019 primary case definition recommended by the Centers for Disease Control (CDC) includes four criteria that must be met to determine a confirmed or probable EVALI case. To rule out infection, the CDC recommends considering testing for the following if clinically appropriate: urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, and HIV-related opportunistic respiratory infections

2019 CDC primary case definition for EVALI	
Confirmed case – must meet all four of: 1. Using an e-cigarette ("vaping") or dabbing in 90 days prior to symptom onset 2. Presence of pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground glass opacities on chest CT 3. Absence of pulmonary infection on initial workup. Minimum criteria are: A negative respiratory viral panel A negative influenza PCR or rapid test, if local epidemiology supports influenza testing All other clinically indicated respiratory infectious disease testing is negative 4. No evidence in the medical record of alternative plausible diagnoses	*Probable case* – must meet all four of: 1. Using an e-cigarette ("vaping") or dabbing in 90 days prior to symptom onset 2. Presence of pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground glass opacities on chest CT 3. Infection identified via culture or PCR, but the clinical team believes this infection is not the sole cause of the underlying lung injury *or* Minimum criteria to rule out pulmonary infection not met (testing not performed), and clinical team believes infection is not the sole cause of the underlying lung injury 4. No evidence in the medical record of alternative plausible diagnoses

and patients failing to improve with supportive measures [25]. Many patients commonly receive initial antibiotics given the possibility of superimposed infection [23–27]. Rarely extracorporeal membrane oxygenation (ECMO) has been required [24, 26, 27]. Patients should avoid any future use of e-cigarette and vaping products. The long-term impact of EVALI on lung health remains unclear at this time. Short-term follow-up studies have shown persistent lung function abnormalities [23, 27] and radiographic opacities [23] in some patients.

Chronic Pulmonary Complications of e-Cigarettes

It is well known that asthmatics who smoke show increased asthma severity, worse asthma control, increased corticosteroid resistance, accelerated lung function decline, and higher asthma-associated mortality [30, 31]. E-cigarettes specifically have been shown to be associated with increased wheezing [32] and asthma symptoms [33]. Additionally, e-cigarettes have been shown to acutely increase airway resistance after use [34, 35], though other studies have failed to show an effect of e-cigarettes on spirometric values [36–38].

There is emerging evidence that incident asthma may be associated with e-cigarette use. Results from the 2016 and 2017 Behavioral Risk Factor Surveillance System (BRFSS) that included over 370,000 participants showed a significantly increased risk of self-reported diagnosis of asthma in daily adult e-cigarette users compared to never smokers (odds ratio 1.81; 95% confidence interval 1.23–2.66) [39]. Another study of 21,618 US adults from the Population Assessment of Tobacco and Health (PATH) study similarly found increased risk of incident asthma among current e-cigarette users (incident rate ratio 1.31; 95% confidence interval 1.01–1.71) [40]. Finally, a meta-analysis of epidemiologic studies showed a significant association between asthma and e-cigarette use [41]. Similar significant associations have been seen in the pediatric population [42, 43], further raising concerns about the public health consequences of e-cigarette use.

There is emerging evidence that e-cigarette use may be associated with COPD, similarly to conventional cigarettes [40, 41]. However, there is also data that for current smokers with COPD, switching from conventional cigarettes to e-cigarettes may have some respiratory benefits including reduction in COPD exacerbations and improvement in physical activity [44]. Switching from conventional to e-cigarettes may also lower the risk of respiratory infections and pneumonia in current smokers [45]. While complete smoking cessation should remain the ultimate goal in the choice between smoking conventional and e-cigarettes, e-cigarettes may have fewer negative effects on the respiratory system in patients with COPD. However clinical data on the full impact of e-cigarettes on respiratory health remains limited. Therefore, further research should be done in this field prior to concluding e-cigarettes are a healthier alternative to conventional cigarettes.

Smoking conventional cigarettes is a well-known primary cause of lung cancer. Given their relatively recent introduction into mainstream use, there are no large retrospective or prospective cohort studies evaluating risk of lung cancer from e-cigarette use. Data from recent in vitro and in vivo studies suggests oncogenic potential [46–48]. Limited evidence also suggests a possible link between e-cigarettes and head and neck cancer [49], though further longitudinal studies are needed to better assess this relationship.

The adverse health effects of e-cigarettes are not limited to current users. The impact of passive aerosol exposure is becoming increasingly recognized. E-cigarettes have been shown to degrade indoor air quality, with levels of indoor particle concentrations from e-cigarettes similar to those of conventional cigarettes [50]. This places nonsmoking bystanders at risk from exposure to secondhand aerosols, which are known to have adverse cardiopulmonary effects [51, 52]. Specifically, secondhand aerosol exposure has been associated with increased risk of asthma symptoms and exacerbations in the pediatric population [33, 53]. Thus, the risks associated with secondhand aerosol exposure from vaping products remains an area in need of ongoing research to better understand their broader effects in population health.

Marijuana

Marijuana is the most commonly used illicit drug in the world [54] and the second most commonly smoked substance after tobacco [55]. In 2019, an estimated 48.2 million Americans (17.5% of the population) aged 12 and older used marijuana in the past year [55]. With the legalization of medical and recreational use in many states, the prevalence of marijuana use in the United States has been increasing over the past decade [54, 55]. However, marijuana remains an illicit substance under federal law, thus limiting research around the potential public health impacts of increased marijuana usage.

Marijuana (also known recreationally as "pot," "weed," "dope," "grass," "hash," "hemp," "ganja," "Mary Jane," and "reefer," among others) comes from the *Cannabis sativa* plant. The drug is usually prepared by drying the flowers and leaves of plant, which contain the cannabinoid ingredients, including 1-delta-9-THC [56]. Consumption of marijuana to generate its psychoactive effects occurs via smoking, vaping, dabbing (inhaling flash-vaporized cannabis concentrates), or ingestion via oral or sublingual routes. Topical use, especially of the nonpsychoactive cannabinoid, cannabidiol (CBD), is also utilized. Cutaneous application of marijuana products does not lead to psychoactive effects and thus is commonly used for medicinal purposes to the locally applied areas. The remainder of this section will discuss inhalational use of marijuana focusing on marijuana cigarette use and its impact on the lungs.

Marijuana smoke is thought to be qualitatively similar in composition to the smoke from tobacco cigarettes, including a significant number of compounds with known carcinogenic, teratogenic, or other toxic effects [57]. However, given that marijuana tends to be smoked differently than cigarettes (e.g., through deeper inhalation, longer breath hold, and performing a Valsalva maneuver at maximal breath hold), the delivery of toxic byproducts has been shown to differ between smoking marijuana and tobacco [58]. As compared with smoking a single filter-tipped cigarette, smoking marijuana has been associated with a threefold increase in the amount of tar inhaled and one third more tar retained in the respiratory tract [59]. Smoking marijuana has also been shown to cause greater carbon monoxide delivery compared to conventional cigarettes [58, 59].

Given similarities in smoke composition, it is not surprising that smoking marijuana has been associated with similar respiratory complaints as with the use of conventional cigarettes, including cough, shortness of breath, wheezing, and chronic bronchitis [60]. However, unlike smoke from nicotine products which acutely increases airway resistance, marijuana smoke has been shown to have immediate bronchodilatory effects [61]. This in addition to the unique way in which marijuana smoke is typically inhaled may explain some of the unique pulmonary manifestations seen in marijuana smokers compared to nicotine-containing cigarette users as described below. Importantly to note, the majority of studies on the pulmonary effects of marijuana use have looked at users who smoke marijuana cigarettes. Findings of these studies may not extrapolate to those who inhale marijuana via

alternative methods, such as vaping, dabbing, or use of a water pipe in which the smoke passes through a water chamber prior to being inhaled. Research on potential consequences of alternative methods of inhalational marijuana use deserves future exploration.

Acute Pulmonary Complications of Inhalational Marijuana Use

Multiple case reports and case series have found marijuana use to be associated with the development of spontaneous primary pneumothorax and pneumomediastinum [17, 62–64]. As described in detail in the previous section on vaping-associated acute lung injury, barotrauma as a result of large swings in transpulmonary pressures during marijuana inhalation is thought to predispose to the development of barotrauma in individuals without underlying lung disease [14].

It has been hypothesized that marijuana is associated with increased risk of pulmonary infection, especially in immunocompromised individuals, as THC has been shown to have immunosuppressive effects [65]. The most widely reported of these associations is the development of invasive pulmonary aspergillosis in immunocompromised marijuana smokers [66–70]. This association is hypothesized to be due to frequent contamination of marijuana with *Aspergillus sp.* [71]. Studies also suggest a link between marijuana use and pulmonary infection in HIV-infected persons [66, 72, 73]. However other epidemiologic studies have not found a significant association [74]. Further large-scale studies are needed to delineate if smoking marijuana independently increases pulmonary infection risk in patients with compromised immune systems.

Chronic Pulmonary Complications of Marijuana

As noted above, marijuana smoke is thought to be similar in content to tobacco smoke with the exception of their active ingredients (cannabinoids and nicotine, respectively). This raises concern that the chronic pulmonary effects of marijuana may be similar to cigarette smoke, such as the risk for development of COPD, lung cancer, and head and neck cancer. However, data on deleterious effects of chronic marijuana use on the lung remain inconclusive at this time.

Research on the long-term effects of smoking marijuana on lung function has not consistently shown significant reduction in forced expiratory volume in 1 second (FEV_1) [75–78] as is typically seen in obstructive lung disease. Studies evaluating for development of airflow obstruction based on reduction in FEV_1/FVC in marijuana smokers have also shown mixed results [61, 76–80]. For studies that have shown reduction of FEV_1/FVC consistent with obstruction, it has been hypothesized that this may be secondary to an observed increase in forced vital capacity (FVC) as opposed to an actual reduction in FEV_1 [75, 76]. Finally, some studies have shown

an increase in lung volumes associated with marijuana use despite the absent development of obstructive lung disease [77, 78]. It has been proposed that this lung volume increase may be related to the repetitive deep inhalation and breath holding typical of inhalational marijuana use, though this hypothesis has yet to be formally studied.

Additional research investigating a link between COPD and marijuana has utilized chest CT to assess for parenchymal damage. While available data is limited to two studies, results have shown minimal emphysematous changes in the lungs of marijuana users alone [81] and conflicting results in those with concurrent marijuana and tobacco use [78, 81].

Taken together, the data seems to suggest that smoking marijuana alone does not significantly increase the risk for development of COPD in the same way that chronic tobacco cigarette use does. Interestingly, studies looking at marijuana concurrent with tobacco use have shown higher rates of COPD prevalence than tobacco use alone [79, 80, 82]. This suggests a potential synergistic effect when these substances are used together.

While the association between the development of COPD in marijuana cigarette users remains unclear, the development of bullous emphysema in young and middle-aged otherwise healthy adult marijuana users has been documented in multiple case reports and case series [83–87]. Chest CT findings include asymmetrical, variably sized emphysematous bullae predominantly located in the upper and mid-lung zones [85]. Not infrequently, the initial manifestation of disease is the development of secondary pneumothorax [84, 85]. Risk factors for development of bullous lung disease remain unclear given the paucity of data, though many cases report a history of concurrent or prior tobacco use [83–85]. There are currently no large-scale epidemiologic studies on marijuana use and bullous lung disease; thus, a true causal relationship between these two entities remains unproven at this time.

There is compelling evidence that long-term marijuana can lead to the development of chronic bronchitis. A recent meta-analysis found moderate to heavy marijuana use was associated with symptoms of chronic bronchitis, including cough, sputum production, wheezing, and shortness of breath [88]. Studies using bronchoscopy to assess airway changes have shown marijuana smokers to have increased tracheobronchial mucosal inflammation and injury similar to tobacco-only smokers [89, 90]. Finally, a 2012 longitudinal study of 299 heavy habitual marijuana smokers followed over a mean 9.8 years found marijuana smoking cessation led to improvement in bronchitis symptoms when compared to ongoing smokers [91]. These findings were redemonstrated in a 2015 longitudinal study that followed 1037 young adults over a 20-year period [92]. In both of these studies, patients who reported marijuana cessation were no more likely to have chronic respiratory symptoms than never smokers at time of follow-up [91, 92], further suggesting a cause-and-effect relationship between development of chronic bronchitis symptoms and heavy marijuana use.

Marijuana as a risk factor for development of lung and head and neck cancers has also been suggested given known carcinogenic components found in marijuana smoke [57]. However, the data around the oncogenic potential of marijuana remains

inconclusive. A 2019 meta-analysis sought to further assess the association between marijuana use and risk of malignancy. Including 25 articles in the analysis, statistically significant increased risk of cancer was only found for testicular germ cell tumors [93]. Research looking at risk of lung and head and neck cancers in marijuana users has shown mixed results (see recent reviews by Jett et al. [94] and Tashkin [95] for comprehensive analyses) with studies often confounded by small sample size, low frequency of marijuana use, or concurrent tobacco use by marijuana smokers.

Despite the known pulmonary effects of inhalational marijuana use described above, the total impact of inhalational marijuana use on lung health remains unclear, and research is ongoing. Marijuana remains an illicit substance under federal guidelines; thus, use may be underreported, and federal regulations around studying marijuana limit research efforts. The only recent legalization for medical use in many US states leads to limited longitudinal data. Studies may also be confounded by concurrent use of additional substances by marijuana users, such as nicotine products or other inhalants. Finally, as previously noted, the means in which marijuana is consumed varies widely. This may impact the potential consequences of use and confound research studies studying lung health outcomes in inhalational marijuana users [56, 96].

Hookah

Hookah smoking, also referred to as water pipe tobacco or *narghile* smoking, is most often used for smoking a specially made flavored tobacco known as shisha. The hookah device consists of a bowl filled with shisha covered by a screen or sheet of perforated aluminum foil. Hot coals sit on top the screen to heat the shisha. Smoke from the shisha passes down through a hollow metal pipe to the base, which contains water. The smoke bubbles through the water and is then inhaled through one or more hoses attached to a mouthpiece. Sessions may vary in length, usually lasting between 30 and 90 minutes [97].

Worldwide, popularity of hookah use has been increasing, with highest prevalence reported in the Eastern Mediterranean Region, which includes Middle Eastern and North African countries [97]. The current overall prevalence of adult use in the United States is unclear. From the most recent 2019 National Health Interview Survey (NHIS), which assesses yearly tobacco use in the United States, 1% of US adults reported current pipe use [98]. Unfortunately, hookah smoking is not differentiated from regular tobacco pipes under this general categorization, making the actual prevalence of hookah use among US adults indeterminate. Data on hookah use among US adolescents is more apparent. Results from the 2019 and 2020 National Youth Tobacco Surveys (NYTS) found an estimated 580,000 middle and high school students reported current use of hookah [99]. Studies have also shown use tends to be particularly high among young adults. The 2018 Monitoring the Future Survey showing nearly 1 in every 7 (13.3%) adults aged 19–28 years had

used hookah during the previous year [100]. Given that use of flavored tobacco products has been shown to increase risk for subsequent tobacco use later in life [101], the increased prevalence of use among adolescent and young adults is particularly concerning.

Leading reasons for hookah smoking include enjoyment of socialization while smoking, multiple available flavors, and the perception that smoking hookah is less dangerous than conventional cigarettes [102]. This latter reason is a common misconception, as studies have shown a number of negative health effects associated with regular hookah smoking including adverse respiratory [103–105], cardiovascular [103, 106, 107], oncologic [103, 108, 109], and infectious disease [110–112] outcomes.

Additionally, the tobacco contained in the shisha increases the risk for nicotine dependence [113]. It has been estimated that daily use of hookah leads to nicotine exposure equivalent to 10 cigarettes per day [114]. The consequences of tobacco exposure through hookah smoking are especially concerning within the adolescent and young adult populations. A recent study showed nicotine dependence symptoms develop at a faster rate in adolescent hookah users compared to cigarette smokers [115]. Further, history of hookah use has been shown to more than double the odds of future initiation of cigarette smoking in adolescents and young adults [116]. Thus, increased public awareness of the harmful and addictive properties of hookah is urgently needed.

As noted above, hookah smoking has known respiratory complications, which will be reviewed in detail below. The harmful effects of hookah come from the smoke, which contain carcinogens and respiratory toxins [117]. Research has shown the volume of smoke inhaled during a 45-minute hookah session is on average 48.6 times higher than that of a single cigarette, leading to increased carbon monoxide exposure [118]. Additionally, hookah smoke has been shown to reduce alveolar cell growth [119] and increase biomarkers of airway inflammation [120] in both in vitro and in vivo models. The adverse effects from smoke are not limited to the user. Hookah lounges, where hookah is frequently used, are associated with high amounts of secondhand smoke [121, 122] and carbon monoxide exposure [123], thereby also putting nonsmoking personnel at increased risk of complication. Thus, the health implications of hookah exposure extend beyond current users and should be recognized by clinicians caring for patients with frequent direct and secondhand exposure to hookah smoke.

Acute Pulmonary Complications of Hookah

Hookah use is known to be associated with several immediate adverse health effects, including vomiting, dizziness, loss of consciousness, and headache [124, 125]. These are thought to be secondary to the high levels of carbon monoxide exposure associated with hookah use [125], and there have been multiple case series documenting carbon monoxide poisoning secondary to hookah [126–128]. Hookah

smoking has also been shown to have immediate effects on the cardiopulmonary system, including acute changes in heart rate, blood pressure, respiratory rate, lung function, and exercise capacity [123, 129–131].

The burden of pulmonary symptoms appears to be increased in hookah smokers. In young adults, hookah smoking is associated with increased respiratory complaints compared to nonsmokers [132]. Even infrequent users report increased symptoms of cough and sputum production [133]. There are case reports linking hookah use to the development of ARDS [134] and eosinophilic pneumonia [135]. Larger epidemiologic studies however are needed to fully understand the risks of hookah use as it relates to acute lung injury.

Hookah use has also been associated with increased risk for spread of infectious diseases. This can occur through sharing of mouthpieces or microbial contamination of the water pipe from incomplete cleaning or sterilization practices after use. A meta-analysis that examined water pipe device microbial contamination found *Flavobacterium*, *Pseudomonas*, coagulase negative *Staphylococci*, and *Streptococcus sp.* to be among the most frequent bacterial contaminants [110]. Transmissible diseases, including tuberculosis [112] and mumps [111], have been documented to spread through the sharing of a water pipe. There is also suspicion that sharing of water pipe mouthpieces could predispose to the spread of pathogenic respiratory viruses, such as *SARS-CoV-2* [136] and Middle East respiratory syndrome coronavirus (MERS-CoV) [137].

Chronic Pulmonary Complications of Hookah

Chronic, habitual use of hookah has been shown to have detrimental effects on lung function similar to cigarette smoking [104]. A meta-analysis evaluating the lung function effects of chronic use found significantly reduced FEV_1 and FEV_1/FVC in hookah smokers when compared to nonsmokers [104]. A cross-sectional study of 110 hookah smokers found more than one third had static hyperinflation as evidenced by residual volumes greater than the upper limit of normal [138].

Given the comparable negative impacts on lung function as chronic cigarette use, it is logical to believe chronic hookah use similarly predisposes to the development of COPD. In a 2017 meta-analysis of five published studies, hookah was shown to be significantly associated with the development of COPD (odds ratio 3.18, 95% confidence interval 1.25–8.08) [103]. There is limited data on the prevalence of COPD in chronic hookah smokers. One cross-sectional study of 245 hookah users in Iran found COPD prevalence to be 10.2%, with increased risk in those smoking ≥3 hookahs per day [105]. It is hypothesized the toxic effects of hookah smoke on lung alveolar cells predispose to the development of COPD via similar mechanisms as smoking cigarettes [139].

A link between hookah smoking and development of malignancy has been more definitively established. Several meta-analyses have shown hookah use predisposes

to the development of lung cancer [103, 108, 109]. Head and neck [103, 108] and esophageal cancers [108, 109] have also been shown to be significantly associated with hookah use. These results are not surprising given the increased exposure to carcinogens that comes from smoking hookah [117, 140].

The increased risk for COPD and malignancy as well as extrapulmonary health complications observed in chronic hookah smokers clearly illustrates that hookah use is not a safer alternative to cigarette smoking as is commonly believed by its users. Greater public health efforts are needed to educate users about the harmful effects of hookah use. Pulmonary physicians also need to be aware of these deleterious health effects and include screening for hookah use in their risk assessments for patients presenting with respiratory complaints.

Other Recreational Inhalants

Recreational use of drugs is widespread. In 2018, an estimated 35.6 million people worldwide were classified as having a drug use disorder. Opioids followed by amphetamines/prescription stimulants, ecstasy, and cocaine were reported as the most widely abused drugs after cannabis [54]. While recreational drugs affect multiple organ systems, inhalational drug use can lead to profound pulmonary manifestations. The following sections will discuss the most common acute and chronic pulmonary effects of both illicit and commercially available recreational inhalants other than cannabis. While some of the drugs or substances discussed may be used for medicinal purposes, this section will focus primarily on recreational use.

Cocaine

Approximately 19 million people globally reported using cocaine in 2018 [54]. The prevalence of use is high in the United States compared to other countries with 2% of the population (5.5 million people) aged 12 and older reporting use in 2019 [55]. Inhalational use of cocaine is common and includes smoking "crack" (also known as "base" or "freebase") cocaine or snorting cocaine hydrochloride powder [141]. Inhalational cocaine users commonly report symptoms of cough, hemoptysis, and chest pain often pleuritic in nature within 12 hours of cocaine use [142]. Coughing up black sputum may also be reported and is secondary to carbon-pigmented macrophages from smoking crack cocaine [143].

Classically, smoking cocaine leads to the acute (within 48 hours) imaging and histopathologic findings of "crack lung." CT imaging typically shows diffuse alveolar infiltrates without pulmonary effusions. Lung histopathologic findings include diffuse alveolar damage, alveolar hemorrhage with associated hemosiderin-laden macrophages, and interstitial and intra-alveolar inflammatory cell infiltrates often

with increased eosinophils. Additional signs and symptoms may include fever, hypoxia, hemoptysis, and peripheral or pulmonary eosinophilia. Corticosteroids may be used for patients with respiratory failure, especially in those exhibiting an eosinophilic inflammatory response [144, 145].

Diffuse alveolar hemorrhage is another common acute clinical manifestation of cocaine use and can occur in the absence of symptoms [146, 147]. Histopathologic findings of elevated hemosiderin-laden macrophages in chronic cocaine users suggest recurrent subclinical hemorrhage is a frequent occurrence [148]. Diffuse alveolar hemorrhage can also occur in the setting of a cocaine-associated vasculitis. This is most commonly associated with the use of the drug levamisole as a cocaine adulterant. Levamisole was previously used in cancer treatments but was withdrawn from the market for human use in 2000 due to adverse effects. Levamisole-laced cocaine is highly associated with the development of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with positive anti-myeloperoxidase (anti-MPO) and/or anti-proteinase 3 (anti-PR3) antibodies. Common manifestations include leukopenia, agranulocytosis, arthralgias, skin lesions, glomerulonephritis, and diffuse alveolar hemorrhage [149–151]. Cocaine-induced midline destructive lesions (CIMDL), or extensive destruction of the osteocartilaginous structures of the nose, sinuses, and palate, can also be seen [152]. In patients who cease cocaine use, symptoms often self-resolve with supportive care alone. Systemic corticosteroids with or without additional immunosuppressants may be used in severe cases or those with organ failure [149, 151].

A variety of additional patterns of pulmonary injury have been reported with cocaine use. Acute pulmonary edema, acute eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, and foreign body granulomatosis secondary to cocaine additives (such as talc, silica, or cellulose) have all been reported [153]. Smoking crack cocaine can lead to bronchospasm and has been associated with life-threatening exacerbations of asthma [154]. Long-term snorting of cocaine can lead to necrosis and perforation of the nasal septum and hard palate [155]. Chronic inhalational use of cocaine has been associated with the development of fibrotic changes in the lungs [148].

Beyond its direct impact on the airways and lung parenchyma, chronic cocaine use is thought to affect the pulmonary vasculature and is considered a possible cause of World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH) [156]. Vascular occlusion from pulmonary granulomatosis in the setting of intravenous cocaine use has been suggested as the etiologic mechanism for cocaine-induced PAH [157]. However, pulmonary vascular abnormalities have also been observed in patients without a history of intravenous use [158]. It is hypothesized PAH from inhalational cocaine use occurs secondary to cocaine-induced pulmonary vasoconstriction leading to chronic remodeling of the pulmonary vasculature; however, there is little evidence to support this hypothesis at this time [159, 160].

Methamphetamine

Approximately 2.0 million Americans aged 12 and older reported use of methamphetamine in 2019. Of those, 184,000 reported initiation of use within the past year, which averages to 510 new users per day [55]. Methamphetamines may be consumed via oral, intravenous, or inhalational (smoking or snorting) routes. The pure form of methamphetamine (also known as "crystal meth" or "ice") is typically smoked and produces the same rapid onset of symptoms as intravenous methamphetamine use [161].

Inhalational methamphetamine leads to similar pulmonary complaints as inhalational cocaine use. Respiratory symptoms often include chest pain and shortness of breath [162], though these may be less frequent than in crack cocaine smokers [161]. Similar acute patterns of parenchymal lung injury have also been reported, including noncardiogenic pulmonary edema, ARDS, diffuse alveolar hemorrhage, and acute eosinophilic pneumonia [163–166]. Increased risk of pneumonia may be seen [167]. Excess free radical generation has been proposed as one potential mechanism to account for the acute lung injury seen with inhalational use of methamphetamines [168].

Unlike cocaine where causation has not been definitively established, methamphetamines are a known cause of WHO group 1 PAH [156] (Fig. 2). A recent cross-sectional study using the US-based Pulmonary Hypertension Association Registry found 22% of the 541 participants had methamphetamine-associated pulmonary arterial hypertension (Meth-APAH) [169]. Compared with idiopathic PAH, patients with Meth-APAH tend to have worse baseline functional status, health-related

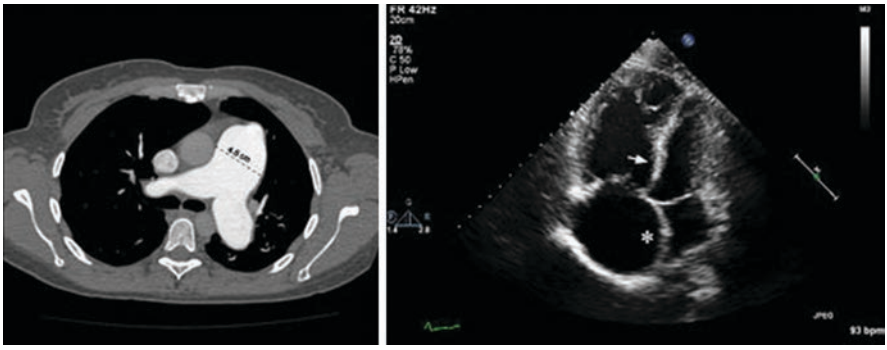

Fig. 2 Imaging from a patient with Meth-APAH secondary to a 20-year history of methamphetamine use. Left panel: CT chest shows a massively enlarged main pulmonary artery measuring up to 4.5 cm. Right panel: Right ventricle (RV) focused apical four-chamber view at end systole from a 2D transthoracic echo shows severe RV dilatation with septal bowing into the left ventricle (arrow) consistent with RV pressure overload. The right atrium is severely enlarged with interatrial septum bowing into the left atrium (*)

quality of life, and right ventricular dysfunction [169, 170] as well as lower 5-year event-free survival despite therapy [170]. The mechanism for development of Meth-APAH remains unclear. Alterations in serotonin signaling leading to arterial smooth muscle proliferation as well as direct damage to pulmonary endothelial cells through the generation of reactive oxygen species secondary to methamphetamine exposure have been postulated as potential etiologic mechanisms [171].

Heroin and Other Opiates

Since 2000, deaths related to drug overdose have been on the rise with the majority involving opioid use. This opioid epidemic has been attributed to rising rates of both prescription opioid misuse and illicit opioid abuse, with heroin and synthetic opioids other than methadone (e.g., fentanyl) primarily accounting for the increased mortality rates [172]. According to the most recent estimates from the 2019 National Survey on Drug Use and Health, 10.1 million Americans aged 12 and older have misused opioids in the past year.

The most commonly abused illicit opioid is heroin. In 2019, an estimated 0.3% of the US population (or 745,000 people) used heroin [55]. "Chasing the dragon," or inhalation of heroin vapor, is the most frequent route of heroin administration by first-timer users [173, 174]. Chasing heroin has been associated with development of respiratory symptoms, such as shortness of breath [175] and bronchospasm in patients with no prior history of airway disease [176]. Heroin smokers have also been shown to have faster annual decline in FEV_1 when compared to nonsmokers and tobacco smokers with COPD [177]. Other reported pulmonary complications of inhaled heroin use include the development of non-cardiogenic pulmonary edema [178], pneumonitis [179], bronchiectasis [180], and acute eosinophilic pneumonia [181].

Consistent with the aforementioned observed accelerated decline in FEV_1, opiate inhalation has been associated with increased risk for development of COPD. A recent 2020 meta-analysis by Hulin and colleagues estimated prevalence of COPD to be 17.9% in people who inhale illicit opiates [182], well above the general population. Further, inhalational heroin abuse has been associated with the development of early-onset emphysema [183]. The exact mechanism leading to increased incidence of COPD in this population is unclear but is hypothesized to be due to pulmonary toxicity secondary to thermal injury, the inhaled opiate itself, the drug's adulterants, and/or synergistic effects from frequent concurrent use of other inhaled agents (e.g., tobacco or cocaine) [183].

Opiate inhalation has also been associated with increased asthma prevalence and complications. The previously mentioned meta-analysis by Hulin and colleagues estimated prevalence of asthma to be 20.2% in inhaled opiate users [182], more than twice the prevalence of asthma in the general US population [184]. More concerning however are the reports of inhaled heroin use being associated with severe and sometimes fatal exacerbations of asthma [185–188]. The bronchospasm elicited by

inhaled heroin is thought to be secondary to heroin causing mast cell degranulation and histamine release similar to other opiates [189]; however, studies have yet to prove this hypothesis [190].

While chasing heroin is the most well-known method for inhalational opioid use, prescription opiates, such as fentanyl and oxycodone, may also be smoked or snorted. There is currently limited research on the pulmonary consequences of inhalational use of these prescription opiates, with the majority of data limited to case reports. There have been several reports of diffuse alveolar hemorrhage from snorting synthetic opioids, including a 45-year-old man that reported snorting fentanyl powder [191] and an 18-year-old male who snorted the fentanyl analog, butyrfentanyl [192], immediately prior to presentation. Pulmonary alveolar proteinosis was reported in a 50-year-old woman who presented with 3 months of shortness of breath that began after she started smoking fentanyl patches [193]. Given the rising rates of synthetic opiate abuse, the full pathologic effects from inhalational misuse of these agents remain to be seen.

Phencyclidine (PCP)

PCP (also known by the street names "angel dust," "crystal," "rocket fuel," "peace pill," and "super grass," among others) is a dissociative anesthetic now commonly used as a recreational drug. In 2011, 6% (75,538 total) of all emergency room visits involving illicit drug use were attributed to PCP, up 106% from just 2 years prior [194]. PCP can be smoked, snorted, swallowed, or injected. When snorted or smoked, it has immediate effects as a central nervous stimulant. The acute pulmonary effects of PCP are largely related to its systemic effects including dyspnea and hyperventilation with shallow respirations. Overdose may lead to aspiration events and/or cardiopulmonary arrest [175].

Commercial and Chemical Inhalants

An estimated 22.5 million Americans aged 12 and older have used an inhalant for its psychoactive purposes at least once in their lifetime [195]. In 2019 alone, an estimated 2.1 million people aged 12 and older in the United States reported inhalant use in the past year [55]. Frequency of abuse is particularly high among adolescents, likely due to ease of accessibility and low cost [196].

Hundreds of commercially available products can produce intoxication when the vapors from these products are inhaled. Commonly abused agents are listed in Table 2. According to the 2015 National Survey on Drug Use and Health, the five most commonly abused agents reported by adolescents were felt-tip pens/markers or magic markers (6.7%); glue, shoe polish, or toluene (1.9%); spray paints (1.7%); gasoline or lighter fluid (1.6%); and computer cleaner/air duster (1.0%) [196].

Table 2 A list of frequently abused commercial and chemical inhalants by category. Where appropriate, both culpable chemicals and the commercial products that utilize these chemicals are listed for completeness. Commonly used street names are listed in parentheses

Commonly abused commercial and chemical inhalants	
Volatile solvents	Correction fluids/white out Dry cleaning fluids Degreaser Felt-tip pens or markers Gasoline Glue Lacquer Nail polish remover Paint thinner or remover Shoe polish Toluene
Aerosols	Air duster/computer keyboard cleaner Air freshener Deodorant Fabric protector spray Hair spray Spray paint
Gases	Butane Ether Halothane Lighter gases Nitrous oxide (“laughing gas, “whippits”) Propane
Alkyl nitrites (“poppers,” “rush”)	Amyl nitrite Butyl nitrite Isobutyl nitrite Isopropyl nitrite Locker room deodorizers

When breathed in through the nose or mouth, inhalants are quickly absorbed via the lungs into the bloodstream leading to an immediate, although short-term, high similar to alcohol intoxication. Overdose can lead to stupor, coma, ventricular arrhythmias, and death. Chronic use has been associated with multiple systemic complications, including learning and memory impairment, peripheral neuropathy, bone marrow suppression, and toxicity to the liver, kidneys, and heart [195].

Given the direct exposure of the airways and lung parenchyma to the inhaled vapors, pulmonary toxicity can also be seen. The prevalence of respiratory complaints associated with inhalants remains unclear given there are few large epidemiologic studies on the adverse pulmonary consequences of inhalants as a general category. A retrospective study of 109 cases of inhalant use reported to the Spanish Poison Control Center between 1991 and 2000 found 2.9% of cases involved respiratory complaints [197]. The most commonly reported respiratory symptoms included nasal congestion and rhinorrhea, cough often productive of sputum, dyspnea, wheezing, tachypnea, chest pain, and exercise intolerance [198, 199]. Reduced FVC and FEV_1 and elevated residual volume have been seen in small studies looking at pulmonary function tests in inhalant abusers [199, 200].

Beyond general respiratory complaints, inhalant use has been associated with direct injury to the upper and lower airways. A multivariate analysis using data from 29,195 respondents in the 2005 to 2007 National Surveys on Drug Use and Health found airway disease, which included bronchitis, asthma, and sinusitis, was positively associated with duration of inhalant use [201]. From occupational health studies, the exposure to high concentrations of isocyanates, such as toluene, has been associated with accelerated decline in FEV_1 as well as the development of asthma [202]. While there are case reports of toluene abuse associated with the development of early-onset emphysema [200, 203], whether the causal relationship between toluene and development of obstructive airway disease extends to abusers of toluene-containing inhalants is unclear.

Additional pulmonary toxicities related to specific inhalants are reported in the literature. Pulmonary hemorrhage has been reported secondary to inhaled tetrafluoroethane found in keyboard cleaner [204]. Volatile hydrocarbons have been associated with the development of Goodpasture's syndrome [205]. All inhalants have the ability to cause a chemical pneumonitis and asphyxiation [198, 206].

Conclusion

Recreational use of inhalants is common among US adults, and the rates of use in adolescents and young adults are rising at an alarming rate. While data is still emerging about the effects of newer recreational inhalants, such as e-cigarettes, it is clear that the use of any inhalant has implications for respiratory physiology and lung biology. Pulmonary complications can be seen with even brief use of an inhalant and can lead to lasting health implications for the user. However, much remains unknown about the long-term risks associated with the use of recreational inhalants. Large epidemiologic studies are needed to better understand chronic pulmonary effects of inhalant use. Research is also needed on the mechanisms of lung injury to obtain greater understanding about the risks associated with individual substances as well as their various methods of use. Finally, clinicians need to be aware of the various pulmonary manifestations of inhalant abuse in order to provide appropriate care and counseling to users of recreational inhalants.

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Pulmonary Hypertension and Air Pollution

Alice Goyanes and Adriano R. Tonelli

Introduction

The impact on the health and well-being of the general population with regard to indoor and outdoor air pollution is an area of increasing attention. The relationship between air pollution and pulmonary disease is well described, as is the association between air pollution on the cardiovascular morbidity and mortality. In fact, a scientific consensus statement published by the American Heart Association in 2010 postulated that particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) has a causal relationship with cardiovascular morbidity and mortality and that exposure to $PM_{2.5}$ is a modifiable risk factor for cardiovascular disease [1]. The relationship between pulmonary vascular disease and air pollution is not as well understood. In this chapter, we will discuss the epidemiology and exposures associated with PH as well as the relationships between RV dysfunction or PH and indoor/outdoor air pollution. We will then take a deeper dive into the proposed molecular mechanisms that could be contributing to pulmonary vasculopathy after a persistent exposure to air pollution.

Pulmonary Hypertension (PH) Definition and Classification

PH is a disease that is hemodynamically defined as a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg [2]. PH can occur as a result of disease in any component of the pulmonary vascular tree (the arteries, capillaries, and veins) or the

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left side of the heart. PH carries with it significant morbidity and mortality. As the pulmonary vasculature remodels and becomes diseased, the afterload for the right ventricle increases, leading to impairment of right-sided heart function, development of right-sided heart failure, and ultimately death [3].

PH is classified according to the 6th World Symposium in PH into five different clinical groups based on the anatomic location where abnormal elevation in vascular resistance develops within the lungs (precapillary and/or postcapillary PH), pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management [4]. PH group 1 disease is called pulmonary arterial hypertension (PAH). PAH is felt to be a pulmonary arteriopathy with vascular remodeling, leading to occlusive vasculopathy, elevation in pulmonary vascular resistance (PVR), dilation of the right side of the heart from pressure and volume overload, and ultimately right heart failure [5]. PAH can be idiopathic, heritable, or associated with a variety of conditions including connective tissue disease, drug or toxins, portal hypertension, human immunodeficiency virus, schistosomiasis, or congenital heart disease. Worldwide, the etiologies of PAH are somewhat different; for example, in the European and North American registries, idiopathic and connective tissue disease-associated PAH are the most common etiologies, whereas Chinese registries report higher rates of PAH due to uncorrected congenital heart disease, and Brazilian registries describe higher rates of schistosomiasis-associated PAH [6].

PH due to conditions other than PAH is more common. In fact, the bulk of PH develops secondary to left heart or pulmonary parenchymal diseases [7]. PH group 2 disease is PH secondary to left heart disease. It is hemodynamically defined as a mPAP greater than 20 mmHg with a left atrial pressure (or their hemodynamic estimation using either the pulmonary artery wedge pressure or left ventricular end-diastolic pressure) higher than 15 mmHg. Left-sided heart diseases that cause PH can include systolic or diastolic left heart failure or valvular heart disease (mitral or aortic). Risk factors for ischemic and hypertensive heart disease are also risk factors for left heart disease-associated PH and therefore augment the clinical probability of having group 2 PH [8].

Group 3 PH is due to parenchymal lung disease and/or hypoxia. PH can be driven by high altitude, pulmonary fibrosis, emphysema, or any other pulmonary disease that causes either significant parenchymal destruction or hypoxia. Worldwide parenchymal destruction from tuberculosis infection is an important contributor to group 3 PH. Notably, indoor and outdoor air pollution contributes to the development of chronic obstructive pulmonary disease as well as other parenchymal lung diseases with hypoxia that can lead to the development of PH [9].

Obstructive PH (group 4 PH) is primarily caused by chronic/non-resolving pulmonary emboli. These unresolved clots cause scar-like tissue that narrows the small blood vessels in the lungs. And the final group on the PH classification (group 5) includes miscellaneous conditions that can affect pulmonary flows, including hematologic disorders (hemoglobinopathies and myeloproliferative disorders), sarcoidosis, neurofibromatosis, fibrosing mediastinitis, and end-stage renal disease [2].

Given this diverse and complex constellation of conditions that drive PH, it is not surprising that the pathobiology is not well understood. Further complicating its understanding is the yet unclear impact of air pollution on the pulmonary vasculature. Interestingly, areas of the world which have the highest burden of indoor (in the form of biomass fuel) and outdoor air pollution have a higher prevalence of conditions associated with PH (of all groups) such as HIV, schistosomiasis, lung parenchymal destruction from tuberculosis, etc. Worldwide, it is estimated that 20 to 25 million people who reside in lower- and middle-income countries have some form of pulmonary vascular disease, and inhabitants of these countries are exposed to high levels of indoor and outdoor air pollution [10]. The appropriate phenotyping of PH in these patients presents important diagnostic challenges, mainly because of the limited access to noninvasive evaluations (blood work, pulmonary function tests, ventilation/perfusion nuclear scan, 6-minute walk, and echocardiography) and invasive hemodynamic assessments (right heart catheterization). Noninvasive testing such as echocardiography is able to provide some insight for suspecting PH, although the precise diagnosis and exact classification of PH is not possible without a right heart catheterization [2].

Pulmonary Vascular Disease and Air Pollution

The largest study to date examining a possible relationship between PAH and air pollution was published by *Sofianopoulo* et al. in 2019 [11]. In this study, which included 300 patients with idiopathic and heritable PAH, both hemodynamics and clinical course were matched up along relative exposure to outdoor air pollution. The investigators used geocoding to estimate annual exposure to $PM_{2.5}$ and nitric dioxide (NO_2) concentrations as the standards for chronic exposure. In addition, they gathered measures of indirect exposure including distance of the patient's home addresses from major roads. Investigators found that exposure to chronic $PM_{2.5}$ was associated with worse transplant-free survival and more than a twofold risk of transplant or death per 3 $\mu g/m^3$ increase in $PM_{2.5}$. Despite this direct relationship between $PM_{2.5}$ and morbi-mortality, $PM_{2.5}$ exposure was inversely associated with a lower PVR. PVR is typically a direct contributor to right ventricular failure and death in PH; however, the association is weak [12]. No association was found between NO_2 levels and PVR or transplant-free survival. Interestingly, proximity from major roads was associated with worse transplant-free survival and hemodynamics.

The relationship between air pollution and morbi-mortality may be related to elevations in the transpulmonary gradient or worse right ventricular function rather than PVR. In a small cohort study of patients with moderate to severe left heart failure and invasive hemodynamic monitoring devices, higher ambient levels of $PM_{2.5}$ were associated with diastolic right ventricular and pulmonary artery pressures [13]. Another observational study of 81 children residing in Mexico City

(which has high levels of both $PM_{2.5}$ and ozone which frequently exceed US air quality standards) showed higher estimated right ventricular systolic pressure on echocardiogram compared to children from another city in Mexico with a lower burden of air pollution [14]. In the Multi-ethnic Study of Atherosclerosis (MESA), a multicenter prospective cohort study of healthy individuals designed to identify risk factors for cardiovascular disease, the investigator identifies a relationship between right ventricular abnormalities on cardiac MRI and nitric dioxide (NO_2) levels [15]. Higher NO_2 levels were associated with higher right ventricular mass and larger right ventricular end-diastolic volume. This direct relationship persisted after adjusting for left ventricular function, levels of inflammatory markers, and underlying lung diseases. Individuals who were exposed for longer periods of time to elevated NO_2 levels had stronger associations between NO_2 and RV mass. Importantly, the development of RV hypertrophy was associated with a threefold risk of heart failure or cardiovascular death in the MESA cohort [15].

Pathobiology of PH and Air Pollution

The molecular basis for the relationship between air pollution and PAH is unknown. The pulmonary vascular pathobiology in PAH is complex and involves vascular remodeling driven by disordered regulation of migratory, proliferative, and apoptotic forces, often influenced by the pulmonary endothelium's ability to release vasoactive mediators and growth factors [16]. These mediators participate in autocrine and paracrine signaling in the endothelium, vascular smooth muscle cells, and surrounding extracellular matrix to influence proliferation, vasoconstriction, and vasorelaxation. Three of the best understood molecular mediators of these functions include endothelin-1 (ET-1), nitric oxide (NO), and prostacyclin, which are pathways exploited to treat PAH.

Endothelin-1 is a potent vasoconstrictor, impacting both the pulmonary and systemic vasculatures. ET-1 is intricately linked to vascular homeostasis by balancing to an extent the vasodilatory actions of NO [17]. In the lungs, ET-1 is released by the pulmonary endothelium and participates in the autocrine and paracrine regulation of the surrounding vasculature including vasoconstriction of the vascular smooth muscle cells. Once ET-1 binds to its receptors, it induces vasoconstriction. Furthermore, ET-1 has mitogenic effects leading to increased proliferation and migration of vascular smooth muscle cells. ET-1 is expressed in higher levels in the lungs of patients with PAH compared to those of patients without PH [18]. Similarly, patients with PAH have higher circulating serum levels of ET-1 than controls [19].

There may be a relationship between ET-1 and air pollution although the evidence is inconsistent. In a study of 27 healthy patients acutely exposed to diesel fumes, there was a rise in serum levels of ET-1 associated with acute vasoconstriction of the peripheral vasculature [20]. In addition, an observational study demonstrated a positive association between average ambient $PM_{2.5}$, daily outdoor time, serum ET-1, and right ventricular systolic pressure (by echocardiogram) in children

residing in Mexico City, a city with high levels of both $PM_{2.5}$ and ozone [14]. Conversely, a small study (n = 13) of healthy young adults found a negative association between serum ET-1 and the natural variations of $PM_{2.5}$ in the air (from low to high levels) [21]. If chronic exposure to high levels of air pollution leads to higher circulating serum levels of ET-1 (and the subsequent vasoconstriction and vascular remodeling stimulated by the endothelin pathway), it may support the potential clinical association between air pollution and PH.

A second mechanism which could contribute to the association between air pollution and PH may be linked to the NO pathway. NO regulates endothelial function and vascular tone in the pulmonary and systemic circulations. NO is a potent vasodilator, inducing vascular smooth muscle relaxation. PAH is a disease of NO deficiency, and in fact both the total body NO and pulmonary NO are lower in patients with PAH compared with healthy controls [22–24]. Lower levels of NO may be in part due to changes in the activity and regulation of the nitric oxide synthases that produce NO. Indeed, the primary enzyme that produces NO in endothelial cells is the endothelial nitric oxide synthase (eNOS). eNOS is expressed in lower levels in lungs of patients with PAH, compared with healthy controls, and the expression level of the enzyme inversely correlates with the degree of histologic changes observed in their pulmonary vessels [25]. eNOS needs to be coupled in a dimer to produce NO, and conditions that promote eNOS uncoupling are noted in pulmonary endothelial cells from PAH patients [26].

Decreased NO bioavailability has been observed after acute particulate matter exposure in several different vascular beds including the aorta, mesenteric arteries, and vessels within skeletal muscle [27–29]. The association between NO levels and air pollution may be explained by eNOS uncoupling or higher clearance of NO. In fact, the inhalation of particulate matter impairs the systemic microvascular endothelium-dependent dilation [28], and the acute exposure to diesel exhaust can lead to eNOS uncoupling, resulting in less production of NO and reduced vasoreactivity [29].

Another possible mechanism which could explain the association between decreased NO bioavailability and air pollution is enhanced NO clearance. Once NO is generated, it may act within the cell or freely diffuse into adjacent cells (e.g., vascular smooth muscle cells), acting as an intra- or intercellular messenger [30]. The NO diffusion may be limited because NO is readily oxidized to the more stable metabolic products nitrite (NO_2–) and nitrate (NO_3) and is scavenged predominantly by hemoglobin [30]. In addition, NO is quickly scavenged through reactions with superoxides and forms peroxynitrite, which then reacts with tyrosine moieties to form nitrotyrosine [31]. In response to nanoparticulate vascular oxidative stress, there is an enhancement of nitrotyrosine in pulmonary and systemic blood vessels, suggesting a more rapid clearance [32] . Therefore, particulate exposure has two separate mechanisms by which NO levels may be affected, either by decreasing production or increased clearance. Given PAH is thought to be a disease of relative NO deficiency, it is possible that the association between chronic exposure to air pollution and PAH may be in part driven by alterations in the NO pathway.

Limitations, Future Study, and Conclusions

While the possible association between air pollution and PH is compelling, there are significant knowledge gaps. Most of the clinical relationships observed between air pollution and PH are associative and therefore missing causality. In addition, present studies are relatively small and lack deep phenotyping, including invasive hemodynamic evaluation, which is currently the mainstay of how PH is diagnosed and classified. The pulmonary vasculature does not exist in isolation; instead, it exists as a part of the circulatory system – so changes to the systemic circulation, left ventricle, and pulmonary parenchyma can lead to PH. Without accurate hemodynamic assessments, it will be difficult to determine if the relationship between PH and air pollution is occurring because of direct or indirect changes to the pulmonary vascular tree.

Furthermore, many of the studies examining the impact of air pollution on molecular mediators of vascular tone were not performed with pulmonary endothelial cells or with models of the pulmonary vasculature (using systemic arterial models instead). The extrapolation of observations made in the systemic to the pulmonary vasculature may not be appropriate. Therefore, before determining if there is a causal relationship (as the American Heart Association has with cardiovascular disease in their 2010 consensus statement), we need to design/conduct studies examining the relationship between air pollution and pulmonary vascular models and the pulmonary endothelium.

In summary, PH is a condition most often secondary to left heart or lung disease. PAH is a rare form of PH characterized by abnormal pulmonary vascular remodeling that carries significant morbidity and mortality. PH is more prevalent in parts of the world with high burdens of indoor and outdoor air pollution. There are multiple observational studies suggesting that there is a relationship between air pollution and higher pulmonary pressures and worse right ventricular function, but clear hemodynamic phenotyping is largely lacking. Air pollution exposure is associated with elevations in the potent vasodilator ET-1 and decreased bioavailability of the key vasodilator NO (Fig. 1). Both ET-1 and NO pathways are intrinsically

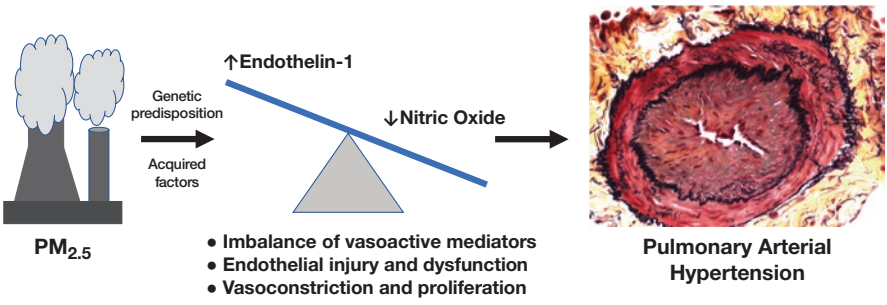

Fig. 1 Schematic demonstrating proposed interplay between air pollution, nitric oxide, and endothelin-1 (molecular modulators of vascular homeostasis) and subsequent development of PH. Photo demonstrates a pulmonary artery with endothelial and vascular smooth muscle cell proliferation, muscularization of the vessel, and narrowing and occlusion of the vascular lumen, all of which are characteristic of PAH

implicated in the pathobiology of PAH, suggesting that these molecules could be involved in the relationship between air pollution and PH.

In conclusion, there is a compelling association between PH and air pollution. Further studies will inform if this association is primarily due to air pollution-induced pulmonary vascular remodeling, through involvement of the NO or ET-1 pathways, and if this is an area where intervention (such as improving indoor or outdoor air quality) can help prevent/improve this very challenging pulmonary vascular disease.

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Climate Change and the Lung Exposome

Christian Cuvillier Padilla and Emily J. Pennington

Introduction

Climate change is bringing forth a series of challenges that will test the mettle of the global medical community in countless ways. The human lung, in particular, will take on a significant degree of burden in the face of a changing global climate system. Through the application of the exposome paradigm to the study of respiratory disease, the onus of environmental exposure in the development of pathology is becoming increasingly understood. In light of the anticipated course of climate change, it seems prudent to explore the ways in which the human exposome will be altered as a consequence and how these alterations may relate to the development of respiratory disease.

Basic Concepts Pertaining to Climate and Climate Change

It may be helpful to begin by defining certain terms and concepts before embarking on further discussion. Climate is the average and expected variability of a multitude of parameters with which we define atmospheric conditions (e.g., precipitation, surface temperature, wind currents, atmospheric pressure) over a certain amount of time, spanning from months to millions of years [1]. In a broader sense, climate is the state and statistical description of Earth's climate system, which can be thought

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of as being made up of five large components: the atmosphere (air), the hydrosphere (water), the cryosphere (ice), the lithosphere (Earth), and the biosphere (life forms). These components are interlocked in a complex series of dynamic interactions that take place to redistribute energy throughout the system. These interactions are influenced by so-called external forcings, such as variable intensities of solar radiation or the effects of volcanic eruptions [1], which have for millennia dictated the state of our planet's climate system.

Greenhouse gases, such as water vapor, carbon dioxide (CO2), methane (CH4), nitrous oxide (N2), and ozone (O3), play another important role in determining the state of our climate system. These gases absorb and radiate energy, exerting an intensifying heating effect on Earth's surface as their concentrations in the atmosphere rise. Throughout the modern climactic era, during which human civilization began and flourished, the concentration of greenhouse gases in the atmosphere was kept relatively stable through the balancing of natural sources and "sinks" (immense repositories, such as the ocean). The dawn of the Industrial Revolution in the mid-eighteenth century triggered a rapid increase in the rate of anthropogenic greenhouse gas production, which has only accelerated over the past century [2]. This external forcing of unprecedented magnitude has brought on a new era of significant human impact on the global climate system that many scientists are calling the Anthropocene—a new geologic epoch with already-observable effects [3].

Climate change is a statistically significant deviation in some of the various parameters of climate lasting for an extended period, typically decades [1]. We are currently undergoing a period of climate change, evidenced perhaps most clearly by the unequivocal consistent warming of our planet's surface. The three-decade span between 1983 and 2012 was almost certainly the warmest period in the last 800 years in the Northern Hemisphere [4]. As one may infer, the anthropogenic component of climate change is becoming ever more sizeable. Human population growth and industry have accelerated anthropogenic CO2 emissions tremendously—the annual rate of increase in atmospheric CO2 over the past 60 years is about 100 times faster than the natural rate of increase seen at the end of the last ice age over 11,000 years ago [5]. This, along with a growing body of additional observations, supports the theory that it is highly likely that humans are responsible for many of the recently observed changes in our climate system [1].

Changes to the Lung Exposome in the Age of Climate Change

Accounting for and analyzing the totality of human exposures from conception to death has proven to be a daunting task and, in this context, will be further made difficult by the rapid pace and vast scope of environmental alterations that will come as a result of climate change in the next century. Climate change can be thought of as leading to acute "extreme" events and other subtler chronic phenomena. Though these two categories of consequences are closely intertwined, it is perhaps easier to discuss them as separate entities when considering their potential effects on the exposome.

Extreme Events

Warming of our atmosphere means that there is an increase in the amount of energy stored in it, which leads to changes in how that energy is redistributed from one climate system component to another. These redistribution mechanisms can lead to extreme weather events, such as tropical cyclones, torrential rains, and heat waves [1]. Climate change is poised to alter the frequency and severity of these extreme events, which will undeniably lead to downstream effects, both acute, such as physical trauma or destruction of stable housing, and chronic, such as disruption of economic activity and post-traumatic stress. This will, through a variety of mechanisms, increase the risk of suffering pulmonary morbidity for many populations.

Perhaps the most dramatic events commonly associated with climate change are the tropical cyclones, referred to as tropical storms, hurricanes, or typhoons, depending on their location and intensity. These meteorological entities form over the warm waters of the tropics and serve as a mechanism for redistribution of heat and moisture to higher latitudes. They consist of a low-pressure central area surrounded by a spiral arrangement of thunderstorms that carry with them heavy precipitation and robust winds and can range in diameter from 200 km to 1000 km [6]. These storms are unfortunately associated with significant costs in terms of material and human losses. The US National Oceanic and Atmospheric Agency (NOAA) designated 2017 as the year with the highest cost ever attributed to hurricanes, after a season in which Hurricanes Harvey, Irma, and Maria battered records and devastated large swaths of the United States [7]. Though there is not a strong body of evidence supporting the notion that hurricanes are becoming more frequent with ongoing climate change [1], the observed warming of our planet's oceans has almost certainly made tropical cyclones more *intense*, a trend that could continue into the future [8], leading to a higher number of major storms impacting land on any given year (Fig. 1). The destructive potential of these storms will be exaggerated by sea level rise, leading to more extensive flooding from storm surge [9]. While there is a recognized risk of acute physical trauma stemming from these events, manifestations of pulmonary disease in this setting will mostly tend to be more insidious, mediated by exposures to perilous environmental conditions.

Storms frequently disrupt the power grids of the regions in their path, leaving many households to depend on devices such as portable generators or gas stoves for vital functions, which can yield subpar air quality. The burning of fuels (e.g., propane, diesel, or gasoline) produces exhaust that increases the concentration of chemical byproducts of combustion in inhaled air for persons in the vicinity. Inhaled carbon monoxide poisoning is a relatively common issue in the United States, leading to more than 400 accidental non-fire-related deaths per year [10], many of which are precipitated by the use of generators in emergency settings. A number of other known byproducts of burning these fuels, such as particulate matter (e.g., $PM_{2.5}$ and PM_{10}), nitrogen oxides, sulfur dioxide, and ground-level ozone, have been associated with an increased risk of developing and exacerbating respiratory disease [11]. The long-term effects of relatively brief exposures such as those experienced during

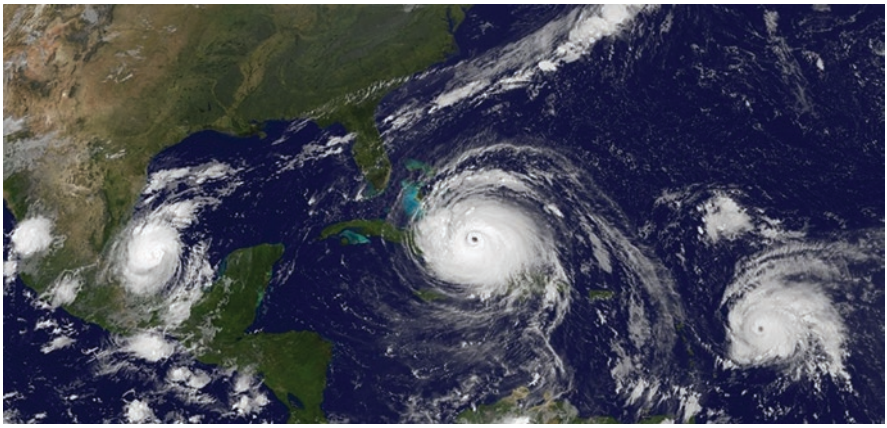

Fig. 1 Satellite image taken during the 2017 Atlantic Hurricane Season, showing Hurricanes Katia (left), Irma (center), and Jose (right) simultaneously churning through the Western Atlantic. Climate change is anticipated to increase the frequency of major hurricanes. (Credit: National Oceanic and Atmospheric Administration (NOAA))

power outages are less clear, so this could be an area of focus for future exposome analyses of tropical cyclone survivors. On occasion, hazardous conditions stemming from these events that we could assume are short-lived can actually be significantly prolonged. Storms can be monstrous and have been associated with destruction of infrastructure so severe that entire populations are effectively cut off from resources such as food, clean water, and electricity for extended periods of time. A recent example of this has already been mentioned in Hurricane Maria, which barreled through the Caribbean in September 2017. The aftermath on the island of Puerto Rico is notable: it is estimated that 100 days after the storm over 1.5 million inhabitants of the island, roughly half of the population, were still without power [12]. Restoration of electric power to the last affected neighborhood was achieved 328 days after the hurricane hit [13], meaning that the use of generators and potential exposure to exhaust fumes was prolonged for many residents of the island.

The unexpectedly protracted Hurricane Maria crisis in Puerto Rico highlighted a number of challenges difficult to fathom in the twenty-first century. Powerful storms, which are theorized to become more frequent as a consequence of climate change, carry the potential to cause massive disruptions to transportation and communication networks. After Hurricane Maria, significant pockets of the population were isolated as mudslides, flooding, and fallen debris left many roads impassable. Difficulties with access were worsened by the destruction of telecommunications infrastructure, an issue that left an estimated over 90% of islanders without cell signal 1 week after the storm [14]. The collapse of infrastructure led to difficulties accessing and storing food, which has been associated with changes in the gut microbiome of children born to mothers who experienced prenatal food insecurity during the crisis [15]. These conditions led to scores of deaths beyond the direct

casualties that perished from injury during the cyclone, most likely attributable to delays and interruptions of medical care [16]. A presumably substantial number of survivors continued to experience delays in risk mitigation, diagnosis, and treatment of their illnesses long after the hurricane had passed. Accounting for these problems in the case of Hurricane Maria and other similar extreme events is made difficult by, among a number of things, the inability to keep adequate medical records in the setting of such widespread devastation. Deficiencies in communication and documentation that are not generally expected in modern times could prove to be a formidable challenge to overcome when applying the exposomic paradigm to the study of these catastrophes.

Tropical cyclones also lead to alterations in the transmission patterns of many infectious diseases, through several mechanisms. Disruption of clean running water by incapacitation of treatment plants and distribution infrastructure is a common occurrence after these events, particularly in developing nations, leaving affected populations dependent on unsafe water sources for basic necessities such as drinking, bathing, and toileting. Development of bacterial and viral enteric disease is a particular concern, but there are effects on the transmissibility of a variety of infectious illnesses of all etiologies, affecting multiple organ systems, following these events [17–20]. Flooding from heavy rainfall and storm surge—which could be amplified by rising sea levels as a consequence of climate change—also poses an increased risk of infectious disease outbreak. Leftover stagnant water pockets create a nidus for reproduction of some species of mosquitoes like *Aedes* (vector for Zika, dengue, chikungunya, yellow fever) and *Anopheles* (vector for malaria, *W. bancrofti*, equine encephalitis viruses). Wading in floodwater can lead to infection with other non-mosquito-borne zoonotic pathogens, such as *Leptospira*, which can lead to pulmonary hemorrhage and acute respiratory distress syndrome and is transmitted via contact with water contaminated by rodent urine. The susceptibility for development of chronic lung disease in survivors of these events could be better characterized by exposome analyses that consider infections after tropical cyclones.

Of course, there are other extreme events associated with climate change besides tropical cyclones. As has already been alluded to in this chapter, climate change has led to a significant rise in global sea levels, driven mostly by glacier and ice sheet loss, a decrease of land-stored water, and ocean thermal expansion. From 1901 to 2010, the global mean sea level rose by approximately 20 cm, with the rate of rise over the past century and a half being larger than the mean rate during the previous two millennia [1]. Sea level rise has the potential to amplify damages brought on by natural disasters that occur through mechanisms unrelated to climate change, such as earthquakes and subsequent tsunamis. Predictions made considering the topography and seismic activity of various coastal regions around the world portend increasingly severe damages from earthquake-triggered tsunamis in the setting of ongoing sea level rise. As an example, a 0.5 m sea level rise is projected to increase the frequency of tsunami-induced flooding by a factor of 1. 2–2.4 in Macau, along the coast of the South China Sea [21]. Findings such as these are particularly concerning to residents of various territories along the seismically active Pacific Ring of Fire, which houses some of the most densely populated areas on the planet. Though

most deaths following events such as these are due to acute drowning or physical trauma, a smaller but significant proportion of casualties stem from the development and exacerbation of respiratory disease. This can occur through a number of mechanisms—from inhalation of particulate matter after the collapse of structures to aspiration of water and the pathogens and contaminants that come along with it. An exceptionally notable example of this is an entity known as "tsunami lung." There are documented cases of near-drowning victims of tsunamis going on to develop severe lower respiratory tract disease believed to be secondary to a combination of chemical and bacterial pneumonias. Sputum culture for bacteria obtained from 2011 Tohoku Tsunami victims yielded isolation of *Stenotrophomonas maltophilia*, *Legionella pneumophila*, *Burkholderia cepacia*, and *Pseudomonas aeruginosa*. Misswallowing of heating oil, gasoline, and machinery oil that was swept up in the tsunami was suspected to play a part in illness as well [22]. In accounts of the 2004 Indian Ocean Tsunami, cases are described that also yielded respiratory cultures of *Burkholderia pseudomallei*, as well as *Nocardia* [23]. While a number of these documented cases develop severe disease requiring endotracheal intubation and mechanical ventilation, it is estimated that a significant amount of mild to moderate cases of tsunami lung go unattended and undiagnosed, leading to unregistered alterations of the exposome.

The 2011 Tohoku tsunami also famously led to the Fukushima Daiichi nuclear disaster, the only event after Chernobyl to be classified as a major accident on the International Atomic Energy Agency's International Nuclear Event Scale, leading to the forced displacement of more than 160,000 persons [24]. A series of events resulting from damage to the plant's infrastructure caused by the massive tsunami wave ultimately released large amounts of radioactive contaminants into the surrounding environment. Despite mitigation efforts, radioactive particulate matter scattered by this incident has been detected throughout the world [25]. Radiation-induced lung injury is another disease entity that has been known to affect workers involved in the mitigation of nuclear disasters [26], leading to pneumonitis in the weeks to months following exposure and fibrosis up to years afterward. Nuclear and industrial waste contamination of the environment can lead to metabolic cascades that increase the likelihood of development of certain malignancies, including lung cancer. Sea level rise could pose a challenge for existing coastal infrastructure of nuclear and other industrial plants, which may have been designed without considering the potentially devastating effects of seemingly small increases in sea level.

The severity and frequency of inland extreme events are also affected by climate change-related alterations in regional weather patterns, meaning that vulnerable populations are not necessarily only located on the coasts. It is highly likely that the number of annual warm days has increased on a global scale as a result of climate change and that, consequently, the number of heat-related deaths has increased in some regions of the world [1]. Heat waves are extreme events that are becoming increasingly problematic. From 1998 to 2017, more than 166,000 people died due to heat waves, with a particularly severe one affecting Europe in the summer of 2003, causing over 70,000 deaths [27, 28]. Between 2000 and 2016, the number of people exposed to heat waves increased by around 125 million [28]. The expansion

of warm climate zones further from the equator means that regions that were previously unexposed to significant heat and, consequently, have not invested in infrastructure that would help moderate its effects (such as air-conditioning systems) may experience increases in heat-related morbidity and mortality. The elderly, children, and those with chronic cardiovascular and respiratory conditions are especially vulnerable during these events, as extremely high ambient temperatures can induce a number of hemodynamic changes and electrolyte imbalances and even airway hyperresponsiveness [29].

Increased average temperature and alterations to precipitation patterns leading to dryer conditions are also causing more frequent and severe wildfires in many regions of the world. Using the Western United States as an example, the frequency of wildfires in the region from 1987 to 2003 was almost four times the average from 1970 to 1986, leading to a total burned area six times larger over the same span of years [30]. The year 2020 saw a number of historic and highly publicized wildfire events around the world, such as the Australian bushfire season, the Amazon and Pantanal wildfires, in addition to the Western US wildfire season. During the 2020 Western US wildfire season, it is estimated that 10.2 million acres (41,000 square kilometers) of land was burned, leading to the destruction of over 10,000 buildings and 46 deaths [31]. In addition to the direct dangers posed to communities in their path, wildfires lead to far-reaching health consequences due to their effects on air quality. Wildfire smoke contains harmful pollutants—nitrogen dioxide, carbon monoxide, and $PM_{2.5–10}$—similar to those discussed earlier in the chapter referring to exhaust fumes. This smoke can travel impressive distances, on occasion being noted as smog in cities a full continent's length away. Associations between wildfire smoke exposure and development or exacerbations of COPD, acute bronchitis, asthma, and pneumonia have been described [30]. Mortality has been found to be significantly increased on smoke-affected days in several cities around the world, and it is estimated that the annual global premature mortality rate due to wildfire smoke exposure is around 339,000 deaths per year [32, 33]. The increasing availability of satellite data and air quality monitoring technology could prove helpful when factoring wildfire smoke exposure into exposomic analyses of respiratory disease.

In facing climate change and associated extreme events, developing nations and socioeconomically disadvantaged communities are disproportionately affected. In the absence of adequate access to resources, adaptation prior to—and recovery after—extreme events is significantly hampered. Difficulties obtaining medications for optimal control of chronic conditions can put certain populations at a baseline elevated risk of exacerbations in the setting of extreme events. Inadequate potable water and food reserves can increase the likelihood of dependency on unsafe sources when the regular chain of distribution is challenged. Housing that is not reinforced to withstand the onslaught of destructive winds or waters is more likely to break down, leading displaced residents to depend on refugee centers burdened by overcrowding and frequently experiencing outbreaks of infectious disease. Refugee status can also lead to lapses in care and monitoring of chronic infections such as tuberculosis, possibly causing outbreaks and drug resistance [34]. Return to damaged housing can increase the likelihood of exposure to cockroaches, molds, and

other particulate matter that has been associated with sensitization and increased incidence of allergic and respiratory disease [35]. The psychological damages inflicted by experiencing traumatic events or subsequent refugee status have been noted to lead to development or exacerbation of a number of psychiatric illnesses including depression, anxiety, and post-traumatic stress disorder, which factor into respiratory health [36–38]. Exposome analyses can be a powerful tool in further defining socioeconomic status as a prominent determinant of health, particularly in the era of climate change.

The Smoldering Consequences of Climate Change

Of course, not all consequences of climate change are reflected in extreme events—there are other, more subtle, effects to be considered. A number of these are in some way outlined earlier in the chapter.

The changes in seasonal weather patterns discussed as pertaining to extreme heat waves and floods will also be responsible for alterations in hydrological systems that set off a cascade of smaller events, infiltrating several aspects of a population's daily life. This is easily illustrated by the plight of the Great Lakes region in North America. The Great Lakes are the largest group of freshwater lakes on Earth by total area and contain 21% of the world's surface fresh water [39]. Climate change poses a slew of challenges to the Great Lakes region which could result in changes to the exposome of those inhabiting it. Increasing spring precipitation and flooding has on occasion delayed planting, which leaves certain crops vulnerable to the hotter, dryer conditions in the summer. Pollination of some crops is also likely to be altered by changes in regional weather. These and other factors may lead to decreasing crop yields—it is anticipated, for example, that yields for soybean and maize will be 10–30% lower by the mid-twenty-first century in the southern Great Lakes watershed [40]. The drive to mitigate these losses can lead to increased use of nitrogen- and phosphorus-containing fertilizers that can contaminate the lakes, a source of drinking water for millions. Elevated concentrations of nitrates in drinking water can lead to methemoglobinemia, with infants being particularly vulnerable (e.g., "blue baby syndrome") [41]. The runoff of these chemicals into the Great Lakes also promotes the surge of algal blooms and massive accumulations of algae that deplete oxygen content and lead to hypoxic "dead zones," where flora and fauna can die off en masse [42]. Algal blooms have caused disruptions for various cities on the Great Lakes coastline, with a relatively recent event cutting off the clean water supply for Toledo, Ohio, in August of 2014 [43] (Fig. 2). Similar events have been catastrophic to marine wildlife off the coasts of essentially all continents, often manifesting as the "red tides," "green tides," and "brown tides" implied in the deaths of sea mammals and fish in large numbers. Unfortunately, these events are projected to become more widespread as surface water temperature increases [44]. The culprit species of algae produce toxins that have been noted to cause neurologic dysfunction, gastrointestinal disease, and respiratory symptoms (such as rhinorrhea, cough,

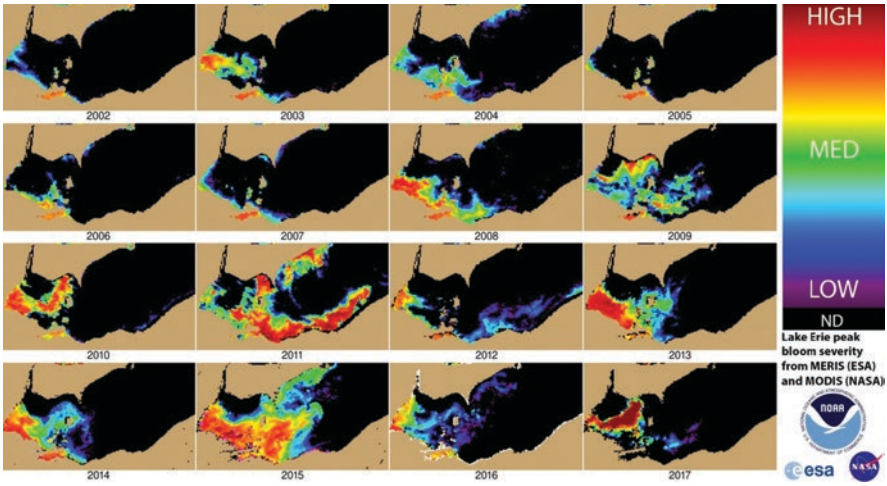

Fig. 2 Satellite images trace the recent history of harmful algal bloom severity in Lake Erie. (Credit: NOAA image using data from the National Aeronautics and Space Administration (NASA) and European Space Agency (ESA))

dyspnea, and wheezing) either via direct exposure or through consumption of exposed marine wildlife [45, 46].

Alterations to seasonal weather patterns can also raise issues for individuals with allergic respiratory disease. Several allergens such as ragweed, tree, and grass pollen have seasonal peaks in airborne concentration that are temporally and spatially affected by several environmental features, such as ambient temperature and concentration of CO2 [47]. Due to changes in regional climate allowing the spread of invasive plant species, it is estimated that the sensitization to ragweed in Europe will more than double (from 33 million to 77 million persons) by the mid-twenty-first century [48], increasing the risk for asthma exacerbations requiring medical attention (Fig. 3). Thunderstorm-triggered asthma is another noteworthy mechanism for exacerbations of airway disease that can be affected by climate change. This refers to several cases of regional surges in acute asthma attacks that have been related to preceding thunderstorms in the affected area. Some regions of the globe will experience more thunderstorms as a consequence of climate change, which puts pockets of populations at increased risk. Though thunderstorm-triggered asthma is a relatively poorly understood clinical entity at the moment, insight has been gained by studying large events, such as the Melbourne thunderstorm asthma epidemic that occurred in November 2016. This event is associated with a 672% increase in respiratory-related presentations to Melbourne and Geelong public hospitals in the 30 hours following 6 PM on November 21st of that year, with an ultimate toll of ten attributed deaths [49]. Surveys of affected patients from that event suggested that history of atopy and rhinitis, increasing age, and suboptimal preexisting asthma control were associated with need for medical attention in the emergency department or hospitalization [50]. It is theorized that thunderstorm-triggered asthma

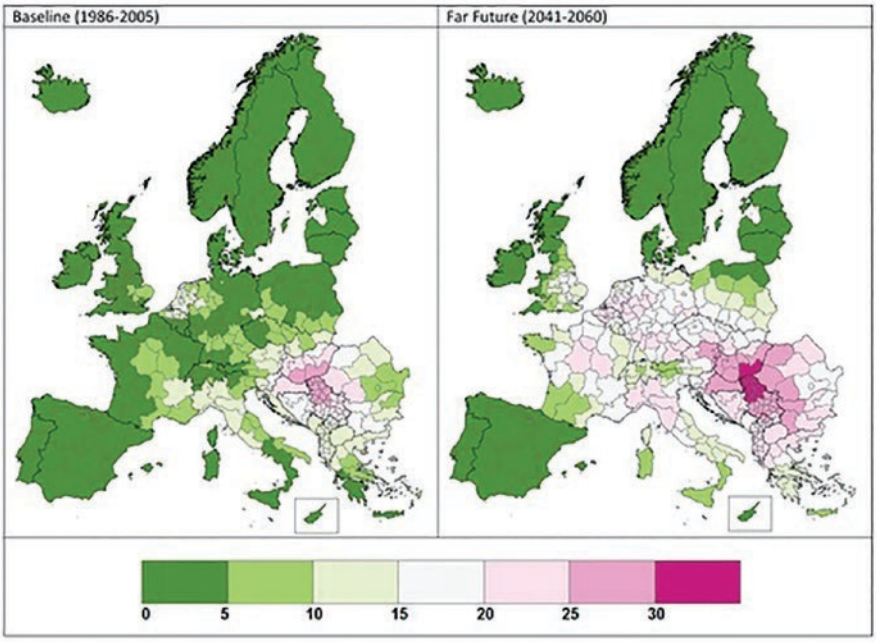

Fig. 3 Averaged results of various models illustrating the percentage of European population sensitized to ragweed pollen at baseline and in the future. (Reproduced from Environmental Health Perspectives with permission from the authors. © EuroGeographics for the administrative boundaries)

events are linked to high concentrations of grass pollen and other aeroallergens at ground level at the time of storms, compounded by rapid changes in ambient temperature and humidity, leading to early bronchospasm responses [51, 52]. While these incidents are quite rare, similar (albeit smaller) events have been recorded in Oceania, Europe, and the United States during the past three decades [52]. With the projected increase in the length of pollen seasons worldwide brought on by climate change [47], and with heightened awareness, it is certainly possible that we will be identifying more events in the future.

The gradual expansion of the tropics and the changes to seasonal rainfall and temperature around the globe will also likely have an impact on the distribution of waterborne and zoonotic infectious diseases [53]. As an example, in China, climate change is projected to significantly widen the area where *Schistosoma japonicum* is endemic [54], which may lead to increased rates of schistosomiasis and secondary pulmonary hypertension. In Europe, climate change has been implicated in the observed dispersion of tick-borne pathogens such as Lyme disease, as the *Ixodes* tick has shifted to elevated altitudes and latitudes. The same was observed in the *Aedes* mosquito, discussed earlier concerning its role in the dispersion of Zika, dengue, and chikungunya viruses [55].

The disproportionate impact of climate change on socioeconomically disadvantaged communities is not limited to the difficulty experienced during and after extreme events. The effect on agriculture, the leading source of income for most of the world's population living in poverty, threatens to disrupt livelihoods and perpetuate inadequate living conditions [56]. The rise in food prices associated with scarcity of crops also mainly impacts the world's poor, which could lead to malnutrition and impaired ability to recover from illness. Economic instability and scarcity of essential resources could lead to increased risk of violent conflict and forced migration, leading to increasing numbers of individuals living in refugee camps, with the subpar hygienic conditions and access to medical care that we have already noted earlier in the chapter. With growing population size in the setting of an outdated energy infrastructure that is in many ways underprepared to face climate change, the issue of energy insecurity also arises [57]. This can lead to pockets of populations either having to resort to unsafe means of energy acquisition (e.g., burning of biomass fuels inside homes for warmth or cooking) or inadequate storage of medications or food that should be refrigerated.

In Conclusion

Climate change is perhaps the most formidable challenge humanity will collectively face in the coming centuries. Though humans have endured periods of climate change in the past, the undeniable influence of anthropogenic radiative forcings on the global climate system has the potential to significantly stretch the adaptability and resilience of multiple populations to the limit of their capacity. Despite global efforts to mitigate the effects of anthropogenic climate change, the scale of the problem is so grand that not much of what we do at this point will prove effective in halting its progression. We are committed to a degree of future climate change as a result of actions that have already occurred, but the course of the next few decades could determine the extent and magnitude of change for the centuries to come [1].

Despite being commonly regarded as a problem for the future, climate change has been causing observable changes to natural dynamics for decades. We can already see how the gradual warming of our climate system has led to more frequent extreme events and disruptions to the lives of millions. With the increasingly recognized impact of the exposome on the course of development of human disease, the modifications to internal and external exposures caused by climate change should become a vital area of study. Through effects on infectious disease pathogenicity and transmissibility, or changes in air quality that trigger altered immune responses, or by the widening of preexisting socioeconomic divides, climate change is undeniably altering the human exposome and will have a noticeable impact on respiratory health.

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