Air pollution and COPD: GOLD 2023 committee report

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Air pollution is a major global threat to patients with COPD. Strong public health policies to reduce air pollution levels along with targeted mitigation strategies are urgently needed. https://bit.ly/3L3dN7e

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Abstract

Exposure to air pollution is a major contributor to the pathogenesis of COPD worldwide. Indeed, most recent estimates suggest that 50% of the total attributable risk of COPD may be related to air pollution. In response, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Scientific Committee performed a comprehensive review on this topic, qualitatively synthesised the evidence to date and proffered recommendations to mitigate the risk. The review found that both gaseous and particulate components of air pollution are likely contributors to COPD. There are no absolutely safe levels of ambient air pollution and the relationship between air pollution levels and respiratory events is supra-linear. Wildfires and extreme weather events such as heat waves, which are becoming more common owing to climate change, are major threats to COPD patients and acutely increase their risk of morbidity and mortality. Exposure to air pollution also impairs lung growth in children and as such may lead to developmental COPD. GOLD recommends strong public health policies around the world to reduce ambient air pollution and for implementation of public warning systems and advisories, including where possible the use of personalised apps, to alert patients when ambient air pollution levels exceed acceptable minimal thresholds. When household particulate content exceeds acceptable thresholds, patients should consider using air cleaners and filters where feasible. Air pollution is a major health threat to patients living with COPD and actions are urgently required to reduce the morbidity and mortality related to poor air quality around the world.

Introduction

Air pollution is a leading health hazard around the world. Globally, it is responsible for 9 million premature deaths per year, corresponding to one in six deaths [1]. Over the past two decades, the mortality rate related to air pollution has increased by 66% owing to a number of factors including increased

industrialisation and climate change [1]. According to the Global Burden of Disease (GBD) Study, air pollution is also responsible for USD 4.6 trillion loss in economic productivity per year and USD 8.1 trillion loss per year in overall health damages (representing 6.1% of global gross domestic product) with >90% of the pollution-related deaths and loss in economic output occurring in low- and middle-income countries (LMICs) [2, 3]. Although cigarette smoking is the leading risk factor for COPD, according to GBD 2019, ∼50% of the risk is at least in part related to air pollution, with the attributable risk amplifying in those living in LMICs [4]. In life-time nonsmokers, air pollution is the leading known risk factor for COPD [2]. Notably, in 2022, the United Nations General Assembly passed a historic resolution declaring that every person in the world has a right to a healthy environment including clean air, water and a stable climate [5]. Given the importance of air pollution in the pathogenesis of COPD [6], the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Scientific Committee commissioned a review of the literature on this topic and provided an update for its 2023 revision [7]. The primary aim of this GOLD report is to provide a strategic direction to improve the care and outcomes of patients living with COPD worldwide.

Methods

Using the search terms “air pollution”, “biomass”, “particulate matter”, “black carbon”, “ozone”, “air quality”, “household”, “indoor”, “domestic”, “COPD”, “chronic obstructive pulmonary disease”, “chronic bronchitis” and “emphysema”, PubMed, MEDLINE and Current Contents were interrogated to 11 February 2023 to identify relevant papers on this topic. In addition, the committee searched reference lists of review papers and published meta-analyses for relevant articles that may have been missed during the electronic search. Finally, experts in the field were contacted to determine whether there were outstanding relevant articles that could be included in this update. As the current report is not meant to recapitulate or replace the many high-quality systematic or qualitative reviews or pooled or meta-analyses that have been conducted on this topic, the interested reader is referred to these articles for details on methodology and findings [8–27].

Definitions

There is no universally accepted definition of air pollution. The World Health Organization (WHO) defines air pollution as “contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere” [28]. Air pollution is a mixture of suspended particles and other chemicals in the air that may harm humans, animals, vegetation or materials [29]. The major classes of air pollution include particulate matter of different sizes, ozone, carbon monoxide, lead, sulfur and nitrogen oxides (NO_x), heavy metals, and other chemicals (*e.g.* polycyclic aromatic hydrocarbons, benzene and acrolein). Among particulate matter, $PM_{2.5}$ consists of fine or ultrafine particles suspended in air that are ⩽2.5 µm in diameter and PM_{10} consists of particles that are ⩽10 µm in diameter. Broadly, air pollution can be divided into household (*i.e.* indoor) and ambient (*i.e.* outdoor) pollutants [28].

Sources of air pollution

Major sources of ambient air pollution include suspended dusts, material abrasion, fossil fuel and biofuel combustion, and agriculture. Fuel combustion generates fine and ultrafine particulates, greenhouse gases (*e.g.* NO_x, methane and carbon dioxide), and other pollutants including black carbon, sulfur dioxide and hydrofluorocarbons [30]. Photochemical reactions between sunlight and NO_x and volatile organic compounds also produce ozone air pollution. Over 2 billion people (most of whom are in low-income countries) still cook, heat or light using solid fuels such as wood, crop wastes, charcoal, coal, dung or kerosene in open fires and simple stoves, which generate very high levels of indoor air pollution, often exceeding the recommended thresholds by 10–100-fold [31]. Since women provide most of the meals in these countries, they are disproportionately impacted by the harmful effects of indoor air pollution [1, 32]. However, this risk may be attenuated with improvements in indoor ventilation, *e.g.* by replacing wood or kerosene stoves with less polluting fuels, such as ethanol or liquefied petroleum gas (LPG), and the use of household air filters (or by installing windows, chimneys, *etc.*, where appropriate) [33, 34]. For example, in one large study in China, installation of a chimney in households where unvented stoves were used for cooking resulted in ∼50% reduction in the occurrence of COPD [35]. Even in industrialised countries, wood burning stoves are still in use today as a source of heat [36]. In the USA, estimates suggest that as many as 30 million persons rely on wood burning as a primary or secondary heating source [37]. It should be noted, however, that there are studies that have not shown clear respiratory health benefits of replacing old biomass burning stoves with more modern LPG stoves [38]. Additional studies are needed to understand the most optimal means of reducing exposures and improving respiratory health outcomes in these communities. Other sources of air pollution include extreme desert or sand storms in hot dry areas,

which can generate a large amount of outdoor particulate matter exposures and cause a significant increase in the rates of hospitalisation and emergency department visits for COPD [39, 40].

Notably, the adverse effects of air pollution on the airways are supra-linear (defined as a dose–response curve that corresponds to greater relative effects at lower doses than implied by linearity), with no "safe" thresholds, contrary to prior beliefs. Even background levels of 2–3 $\mu g \cdot m^{-3}$ of $PM_{2.5}$ are associated with a higher mortality compared with regions that have even lower levels [41]. While these data reflect "chronic" or "long-term" effects of fine and ultrafine particles in the atmosphere, significant variations can occur throughout the year, especially during periods of extreme weather. The harm imposed by particulate matters is related to their size, structure and composition (*e.g.* highly acidic particles are more harmful) [6].

Based on current trends, global climate change, defined as long-term shifts in worldwide or regional climate patterns, will have profound consequences for air quality throughout most of the world, and the interested reader is referred to a report by Romanello *et al.* [42] that details the economic and health impact of global warming. Briefly, the Earth's temperature has risen by an average of 1°C since 1900. The annual rate of global warming has doubled since 1980 (0.18°C per year) and the 10 warmest years in historical record have all occurred since 2010. Since the turn of the 21st century, the annual heat-related death rate in persons >65 years of age has increased by 68% owing to global warming. With the current policies, the average temperature across the world is expected to increase by 2.7°C by the end of the century [43]. In one modelling study, Hong *et al.* [44] showed that the projected climate change over the next 30 years will increase the levels of particulate matter and ozone in the atmosphere by 3–4% in China, even if there is no increase in the size of the population or any meaningful changes in air pollutants that are produced. Based on these projections, the number of Chinese adults dying from $PM_{2.5}$ and ozone exposure is expected to increase by 100–300% by 2050 [44]. Climate changes may also promote the occurrence of wildfires and dust storms and extreme weather-related events such as heat waves (that are expected to become more frequent and longer in duration) and atmospheric stagnation that can result in dramatic reductions in air quality [45]. Wildfire smoke, for instance, contains a variety of substances that are harmful to human health, including $PM_{2.5}$, carbon monoxide, NO_x and benzene. In some cases, during wildfires, the levels of $PM_{2.5}$ can exceed 500 $\mu g \cdot m^{-3}$ in areas whose 1-year mean average is typically $\leqslant$25 $\mu g \cdot m^{-3}$ [46]. In Canada, it is expected that extreme weather events could increase by as much as 200–300% in eastern parts of the country and by ~50% in Western Canada over the next century [47], a scenario that is likely to be paralleled in other parts of the world [48]. In other regions, air pollution from peat burning and other biomass materials imposes significant health risks to residents. In large densified urban settings where there is often significant replacement of vegetation for concrete and asphalt for roads, buildings and other modern structures, rapid heating of surfaces can occur during heat waves, leading to a heating island effect and heat-related deaths, especially in apartments and care homes for the elderly [49]. The adverse effects of air pollution are summarised in box 1.

Air pollution and COPD pathogenesis

Air pollution is an important contributor to the pathogenesis of COPD (box 2). A recent systematic review and meta-analysis showed that a 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ levels was associated with an 18% increase in the incidence of COPD (pooled hazard ratio 1.18, 95% CI 1.13–1.23), while ambient PM_{10} or nitrogen dioxide levels did not significantly relate to the risk of COPD [9]. In one of the largest studies to date, Doiron *et al.* [50] used the UK Biobank database and showed in a cross-sectional study of 303 887 individuals aged 40–69 years that exposure to air pollution significantly increased the risk of COPD (OR 1.52 per 5 $\mu g \cdot m^{-3}$ increments in $PM_{2.5}$ and OR 1.12 per 10 $\mu g \cdot m^{-3}$ increments in nitrogen dioxide). However, exposure to ambient coarse particulate matter (2.5–10 µm in diameter) air pollution was not associated with the risk of COPD, highlighting the potential importance of small particles and gases in the pathogenesis of COPD [50]. Similar findings were noted by Shin *et al.* [51] using population-based data from Ontario in Canada, and Liu *et al.* [52] using a pooled dataset of three cohorts in Denmark and

BOX 1 Impact of ambient air pollution on respiratory health in patients living with COPD: key messages

- There are no "safe" levels of ambient air pollution [41, 106]
- The relationship between air pollution levels and respiratory events is supra-linear [106]
- Wildfires and extreme weather events such as heat waves are major threats to COPD patients, and acutely increase their risk of morbidity and mortality [46]
- Over the next 30 years, the number of persons dying from air pollution exposure is expected to increase by 100–300% owing to climate change [44]

BOX 2 Impact of ambient air pollution on patients living with COPD

- Approximately 8% of global COPD deaths may be attributable to air pollution [28]
- Air pollution exposure is associated with increased risk of COPD and accelerated decline in lung function [50, 58, 107]
- The risk is amplified in patients with small airways abnormalities (*e.g.* those with dysanapsis), in females and in concurrent smokers [50]
- Chronic exposure to high levels of air pollution impairs lung growth in children [59, 60]
- Air pollution exposure acutely exacerbates patient symptoms and reduces lung function [20]
- Acute increases in air pollution may also increase patient susceptibility to respiratory tract infections [94]
- Excess cardiovascular mortality related to $PM_{2.5}$ exposure may preferentially affect COPD patients owing to a high prevalence of cardiovascular disease in these patients [77]

$PM_{2.5}$: particulate matter ⩽2.5 µm in diameter.

Sweden where they observed a supra-linear relationship of incident COPD with ambient concentrations of $PM_{2.5}$, nitrogen dioxide and ozone. However, there have also been dissenting studies [53, 54].

It should be acknowledged that although COPD has been well defined in previous studies, there were major limitations to the definition and measurement of household air pollution that have been used in these studies. Thus, it has been difficult to disentangle the effects of household air pollution from other features of poverty, which may also associate with COPD. Furthermore, many prior studies on this topic have been methodologically challenged by a number of factors, including the use of a cross-sectional (rather than longitudinal) design, which have limited causal inferences [55]. However, there have been some notable exceptions.

Using a longitudinal design, Kariisa *et al.* [56] demonstrated that long-term exposure to $PM_{2.5}$ increased symptoms and accelerated lung function decline over 5 years in 1218 patients with very severe COPD. Even short-term exposures to high levels of ambient $PM_{2.5}$ and PM_{10} exacerbated patient symptoms and reduced lung function [57]. In the largest study of its kind, Guo *et al.* [58] evaluated 285 046 participants aged ⩾20 years, who were part of the Taiwan Health Management Institution cohort, to determine the effects of air pollution on lung function trajectories over time. Using a satellite-based spatiotemporal model to estimate the 2-year average ground concentration of $PM_{2.5}$ for each participant's residential area, they found that every 5 $\mu g \cdot m^{-3}$ increment in $PM_{2.5}$ was associated with a reduction in forced vital capacity (FVC) of 1.18%, forced expiratory volume in 1 s (FEV_1) of 1.46% and FEV_1/FVC ratio of 0.21% relative to baseline levels. Annually, this increment in $PM_{2.5}$ exposure accelerated the decline in FVC by 0.14%, FEV_1 by 0.24% and FEV_1/FVC ratio by 0.09% from baseline levels. Accordingly, the risk of COPD over time increased by ∼40% for persons living in the most polluted areas compared with those living in the least polluted areas (by quartiles). This risk was further increased in women and smokers [58]. Children (<10 years of age) may be particularly susceptible to the harmful effects of air pollution. For example, a study from the UK showed that chronic exposure to small particulate matter (<1.0 µm in diameter) was inversely related to the lung function of children 8–12 years of age; interestingly, this relationship was largely explained by the presence of black carbon particles in airway macrophages of these children [59]. In a cohort of 2164 children 8–9 years of age, Mudway *et al.* [60] showed that children's FVC was inversely related to the ambient concentrations of NO_x and PM_{10} in their homes or school, suggesting that air pollution impairs lung growth in children. As ∼50% of adult COPD is attributed to poor lung growth either *in utero* or in childhood, the clinical impact of poor air quality today may continue to be felt for many decades from now [61]. A systematic review evaluating the impact of biomass smoke on the occurrence of COPD showed that despite heterogeneity across the studies, exposure to solid fuel smoke on average more than doubled the risk of COPD and chronic bronchitis (OR 2.80, 95% CI 1.85–4.0 and OR 2.32, 95% CI 1.92–2.80, respectively) [25]. While the pathophysiology of pollution-related COPD is unknown, there is growing evidence that small particles drive a low-grade inflammatory process (mediated by macrophages) in the small airways leading to bronchiolitis [62].

The data supporting the relationship between air pollution and poor COPD outcomes is most robust for fine or ultrafine particulate matter [63]. The relationship between other common constituents of air pollution such as nitrogen dioxide, sulfur dioxide and carbon monoxide and patient symptoms or decline in lung function is less well established [64]. In general, the adverse impact of air pollution on COPD outcomes is amplified in those with other known risk factors for COPD, such as cigarette smoking, asthma or low socioeconomic status [65].

Some studies have assessed the impact of ambient air pollution on the two important phenotypes of COPD, *i.e.* emphysema and small airways disease. To determine the impact of air pollution on emphysema, WANG *et al.* [66] examined data from 5780 adults in the USA, who participated in the MESA study. In cross-sectional analyses, the ambient concentrations of ozone, $PM_{2.5}$, NO_x and black carbon were related to the extent of emphysema on baseline computed tomography (CT) scans. In longitudinal analyses, ambient concentrations of ozone and NO_x but not $PM_{2.5}$ accelerated the progression of emphysema as quantitatively measured on thoracic CT scans over 10 years of follow-up [66]. These data suggest that the gaseous component of air pollution may have a greater impact on emphysema pathogenesis and progression, while fine and ultrafine particles may have a larger influence in the small airways [67]. In a recent study using data from the Lifelines Cohort Study, DOIRON *et al*. [68] found that long-term exposures to ambient nitrogen dioxide and black carbon but not $PM_{2.5}$ were associated with increased odds of both prevalent and incident chronic bronchitis [68]. Higher effect sizes are generally observed in women, never-smokers and younger individuals [32, 69]. Chronic bronchitis has also been reported with inhalational exposures to dusts, biomass fuels, chemical fumes or domestic heating and cooking fuels [70]. Notably, previous studies suggest that exposure to biomass smoke is associated with a predominance of airway disease, whereas long-term tobacco smoke exposure is typically associated with both emphysema and small airways disease [32, 69].

While these observational studies provide strong evidence for the association of air pollution with the risk of COPD, owing to potential confounders and methodological biases, causality remains elusive. To address this gap in knowledge and to investigate impacts of short-term exposure to ambient air pollution on lung function and respiratory symptoms, SINHARAY *et al.* [71] performed a randomised, cross-over study where the investigators recruited 40 individuals with COPD, 40 healthy volunteers and 39 patients with ischaemic heart disease, and asked the participants to walk for 2 h along either Oxford Street (a commercial area) or Hyde Park (an urban park) in London in the UK. Air pollution levels, which included black carbon, nitrogen dioxide, PM_{10} and $PM_{2.5}$, were significantly higher on Oxford Street than in Hyde Park. Whereas healthy volunteers did not report any significant changes in symptoms during their walk, patients with COPD or ischaemic heart disease indicated greater symptoms, including cough, wheeziness and dyspnoea, while walking on Oxford Street. Importantly, patients with COPD demonstrated a significant reduction in FEV_1 and FVC following their walk, which related significantly to the extent of their exposure to $PM_{2.5}$ and other ultrafine particles during their walk [71]. This relationship, however, was not observed in patients with ischaemic heart disease or healthy volunteers [71]. These data are in general agreement with those of PEACOCK *et al*. [72], who showed a strong association between short-term ambient air pollution exposure and patient symptoms, including dyspnoea [72]. This study, however, did not measure ambient particulate matter or ultrafine particles, which appeared to be most strongly related to impairment in lung function in the SINHARAY *et al.* [71] study. Collectively, these data provide strong evidence that short-term exposure to particulate air pollution leads to worsening of symptoms and reductions in lung function in COPD patients. However, analyses with longitudinal data are still needed to further examine the causal relationships of air ambient pollution and its components to decline in lung function and risk of COPD.

Air pollution and exacerbations of COPD

Patients living with COPD are susceptible to (even modest) acute increases in air pollution levels and to extreme changes in weather, which may be seasonal or sporadic. Thus, acute increases in air pollution are major contributors to exacerbations of COPD. A systematic review in 2016 identified 59 primary studies on this topic and in aggregate found that acute reductions in air quality were associated with increased risk of COPD exacerbations [20]. For the gas constituents of air pollution, the relationships with COPD exacerbations were the strongest on the first day of exposure, whereas for the particulate matters, the relationships were the strongest 3 days after the peak exposure [20]. Interestingly, investigators of the East London COPD cohort, who followed patients from 1996 to 2015, found a significant association between ambient concentrations of NO_x and increased risk of viral-type but not bacterial-type exacerbations [73]. This relationship was most notable 2–4 days following the peak exposure and those exacerbations associated with higher ambient NO_x levels took longer to recover.

In a study in China, LIANG *et al.* [74] used data from 35 monitoring stations across Beijing to determine the relationship between air pollution and risk of hospitalisations related to an exacerbation of COPD. They found that the relationship was positive such that the highest risk of hospitalisation occurred on days with the highest ambient concentrations of PM_{10}, $PM_{2.5}$ and gases such as sulfur dioxide. Interestingly, these relationships were only statistically significant during the warm season (May to October) and particularly notable in those ⩾65 years of age and among women [74]. Similar findings were noted in the USA. Using Medicare data of 11.5 million recipients, DOMINICI *et al.* [75] found that a short-term 10 $\mu g \cdot m^{-3}$ rise in ambient $PM_{2.5}$ was associated with a 2.6-fold increase in the risk of COPD-related hospitalisation.

Exposures to indoor air pollutants (*e.g.* dust mites, cockroaches, cat or dog dander, or mouse droppings) may also provoke exacerbations of COPD. One study showed that patients with indoor exposure and sensitisation to these antigens had lower lung function, worse symptoms and a greater risk for exacerbations [76].

Air pollution and mortality

Exposure to ambient $PM_{2.5}$ was the fifth-ranking mortality risk factor in 2015. Deaths attributable to ambient $PM_{2.5}$ increased from 3.5 (95% uncertainty interval (UI) 3.0–4.0) million in 1990 to 4.2 (95% UI 3.7–4.8) million in 2015 [77]. Exposure to ozone caused an additional 254 000 (95% UI 97 000–422 000) deaths [77]. In 2012, the WHO estimated that ∼8% of global COPD deaths were attributable to air pollution [28]. In 2015, Maji *et al.* [78] examined $PM_{2.5}$-related mortality in China and found that ∼12% of these deaths were related to COPD. A modelling study in China showed that an average 10 $\mu g \cdot m^{-3}$ increase in ambient $PM_{2.5}$ levels was associated with ∼1% increase in mortality in Beijing and surrounding regions [79]. One study in the USA showed that during wildfire smoke-filled days, the risk of COPD mortality increased by 14% [80]. Thus, mitigation strategies (as discussed later) are needed to reduce morbidity and mortality during episodes of poor air quality.

It should be noted that >50% of excess mortality related to $PM_{2.5}$ exposure is cardiovascular in nature [77], and many COPD patients have cardiovascular comorbidities and are thus susceptible to not only respiratory mortality but also those related to ischaemic heart disease and stroke. Furthermore, it has been demonstrated that cardiovascular risk in adults with COPD has a supra-linear relationship such that hazard ratios for mortality per 10 $\mu g \cdot m^{-3}$ of $PM_{2.5}$ are highest at lower concentrations [6, 81]. Thus, the overall mortality related to $PM_{2.5}$ exposure is much higher than that focused on respiratory causes [82].

Proposed molecular mechanisms and pathways

The effects of air pollutants on the respiratory system have long been studied. $PM_{2.5}$, nitrogen dioxide and ozone have irritant effects, which can acutely provoke bronchial hyperreactivity, cough and sputum production [6]. However, the exact mechanisms by which air pollution causes COPD or exacerbations have not been fully elucidated. A principal mechanism of action may occur at the level of the respiratory epithelium lining the airway [83] with air ambient pollutants inducing the release of interleukin (IL)-8, a pro-inflammatory chemokine, and other molecules which attract neutrophils, monocytes and macrophages to the airways [84, 85].

Chronic exposure of rats to small particulate matter for 7 months induces changes in the airways consistent with COPD such as mucus hyperplasia, airway remodelling and emphysema [86]. Air pollution particles contain many reactive oxygen species (ROS) that can damage the airway epithelia and cause a dysregulated immune response in the host unless these molecules are counterbalanced by a series of antioxidants [87, 88]. Interestingly, individuals with certain genetic variants in the antioxidant enzyme generating genes such as those for glutathione transferase (*e.g. GSTM1*, *GSTP1*, *GSTT1*, *etc.*) and quinone reductases (*e.g. NQO1*) may have increased predisposition to pollution-related lung injury when these enzymes are reduced in quantity or quality [89]. Air pollution-related ROS may also cause mitochondrial dysfunction in epithelial cells, which in turn increases cellular production and exposure to ROS, creating a vicious cycle. Air pollution components can also cause mucociliary dysfunction, enhance both airway and systemic inflammation, perturb autonomic balance to activate neuro-humoral forces, and unleash a cascade of endogenous secondary messengers such as oxidised lipids [82]. Moreover, air pollution components can induce changes in the epigenome especially in genes that drive type 2 inflammation such as *IL4* and *IL13* [90], which may be involved in COPD exacerbations. A recent mechanistic study showed that patients living with COPD may be more susceptible to poor outcomes when exposed to air pollution because they harbour persistent low-grade local and systemic inflammation and demonstrate immune dysregulation including an imbalance in helper T-cell subsets (Th1 and Th2) that results in an aberrant immune response when challenged [91]. It should be noted that solid components of air pollution can persist in the lungs for decades, usually in macrophages, even among nonsmokers. A recent study has shown that tissue macrophages take up air pollution particles and these particles may reside in the macrophages (especially those with cell surface markers $CD68^{+}CD169^{-}$) for decades. Importantly, once these macrophages take up the particles, they partially lose their phagocytic function, which is essential for maintaining tissue homeostasis [92].

Recent evidence also suggests that the small airway anatomy in COPD could predispose patients to the harmful effects of air pollution [93]. Air pollution may also enhance COPD patients' risk for respiratory infections, leading to exacerbations [20], pneumonia [94] or coronavirus disease 2019 (COVID-19) [95]. Although the mechanisms underlying these observations are largely unknown, small particulate matter in

air pollution may act as a carrier for microbial pathogens to the airways. Air pollution can also upregulate certain receptors for respiratory viruses and impair interferon-related defence mechanisms in the airways, enabling pathogens to invade the host [96, 97]. The proposed molecular mechanisms and pathways are summarised in figure 1.

Mitigation and management strategies

Reduction in ambient air pollution is a key goal in the prevention and management of COPD.

Increasing actions are required to further intensify international air pollution regulations given that patient populations living in countries even with relatively low air ambient pollution may still be susceptible to acute episodic relative increases in air pollutant concentrations. The WHO currently recommends annual average concentrations of $PM_{2.5}$ to be $\leqslant 5\ \mu g \cdot m^{-3}$ and annual average concentrations of PM_{10} to be $<15\ \mu g \cdot m^{-3}$; annual average ozone levels should be $<60\ \mu g \cdot m^{-3}$, nitrogen dioxide $<10\ \mu g \cdot m^{-3}$ and sulfur dioxide $<40\ \mu g \cdot m^{-3}$ [98]. Regrettably, 97% of the world's major cities fail to meet these standards and no country currently meets all of these thresholds [98]. As air quality is determined largely at a regional or

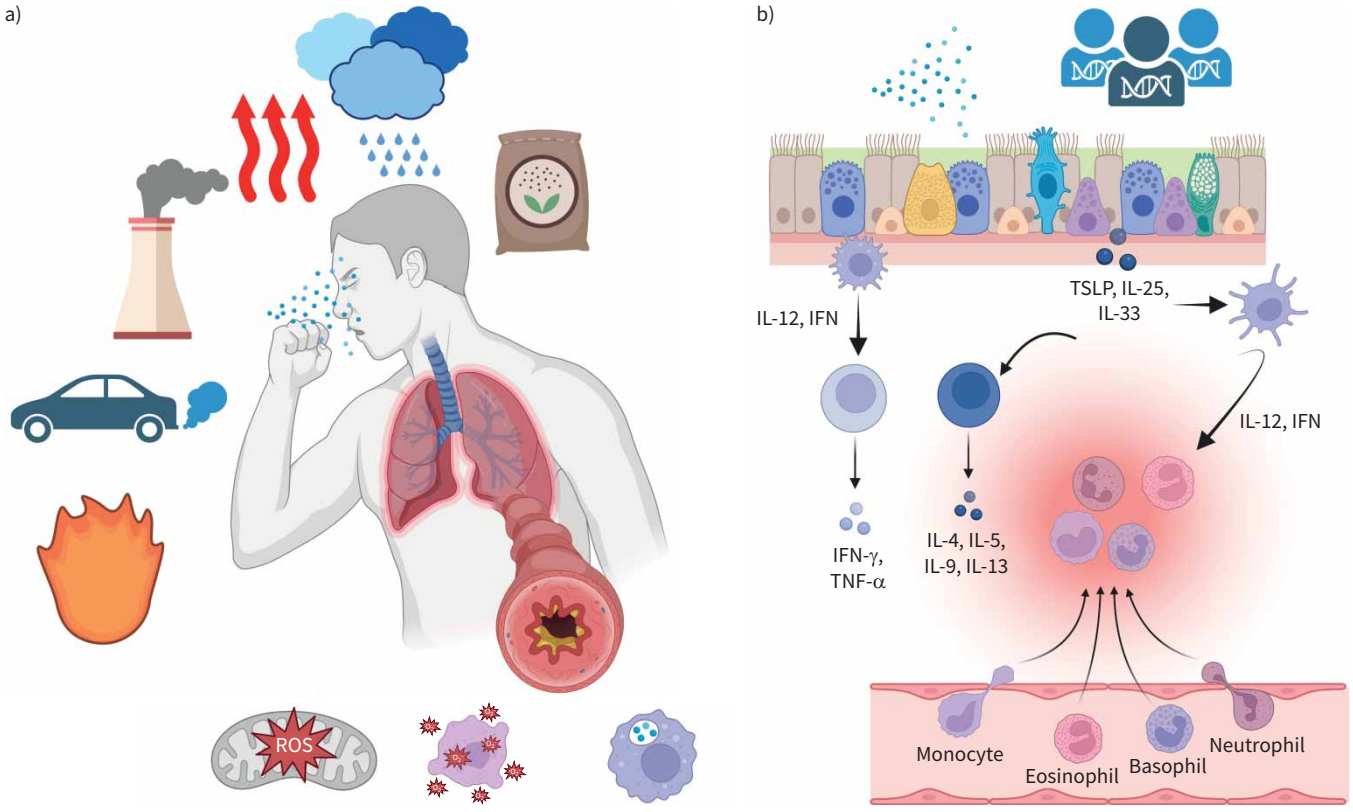

FIGURE 1 A proposed model of how air pollution may harm the airways, leading to COPD. a) Indoor or outdoor air pollution particles and gases (from various sources including combustion of fossil or biomass fuel, wildfires, climate change and extreme weather events) enter the upper and then the lower airways during respiration. Initially, gases move in bulk flow and then more distally gas transport occurs *via* molecular diffusion, thus exposing small airways and alveoli to their harmful effects [109]. While the exact pathogenic mechanisms are largely unknown, air pollution constituents may cause mitochondrial dysfunction, accelerated cell death and tissue remodelling, secondary to the build-up of reactive oxygen species (ROS), especially in mitochondria and immune cells, and inflammation (both type 1 and type 2) in genetically susceptible individuals. Interestingly, air pollution particles may accumulate in tissue macrophages, especially near draining lymphatic tissue and "live there" for decades [67, 92], which may perpetuate the inflammatory process. Overall, the impact of air pollution appears to be greater for airway disease than parenchymal disease [32]. b) An overview of how air pollution particles may induce inflammatory changes in the airways of susceptible persons. Epithelial cells are the major source of alarmins (thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 and IL-33), which stimulate lymphocytes, coercing them to produce IL-4, IL-5, IL-9, IL-13 and other type 2 cytokines, and type 2 innate lymphoid cells are the major source of IL-12 and interferon (IFN), which in turn skew the T-lymphocytes towards a type 1 phenotype, equipping them to secrete more IFN, tumour necrosis factor (TNF)-α and other type 1 cytokines. These cytokines play an important role in the recruitment of circulating immune cells into the airways, establishing an inflammatory cascade and ultimately airway remodelling. Th: T-helper cell. Figure partially created with Biorender.com.

country level (or beyond), the establishment and enforcement of strong policies and regulations are needed. Some of these policies may include: transition of coal and gas power stations and diesel generators to solar, wind and hydropower; rapidly expanding public transport and promoting active transportation (walking and cycling) over cars in urban areas, reducing toxic emissions from industrial sources and vehicles and engines through stringent emission standards and cleaner burning gasoline (and replacing conventional automobiles with electric vehicles where possible); avoidance of coal and wood burning for home heating or cooking; installation of efficient stoves and chimneys; and various soil conservation and carbon sequestration interventions in agriculture. It is essential that after implementation of air pollution reducing policies, these interventions should be rigorously evaluated as there may be unintended consequences of these policies. For example, while a new traffic policy in Rome in Italy significantly reduced traffic-related air pollution across all jurisdictions, most of the health benefits were observed in those living in high-income areas [99].

Reduction in air pollution levels has not only important health benefits for patients living with COPD but also for lung development (and thus impacting future incidence of COPD). In the Children's Health Study, for example, which was conducted in Los Angeles in the USA, long-term improvements in air quality were associated with (clinically significant) positive effects on lung function growth in children, after controlling for important confounders [100].

Air pollutant public broadcast warnings and advisories may also be useful when nitrogen dioxide and $PM_{2.5}$ concentrations are measured to be higher than typical values, and with the advent of "apps", this information can be personalised (*e.g.* smartphone apps for individual high-risk patients to specifically alert them). On heavy exposure days such as during wildfires, indoor $PM_{2.5}$ levels are ∼20% of those measured outdoors [101]. When air quality is poor, patients living with COPD should thus avoid outdoor activities and perform daily activities indoors, provided that indoor air quality is acceptable [102]. There is an ongoing controversy on the merits of wearing a face mask to reduce the health hazards of air pollution, which has been reviewed in detail by Chen *et al.* [103]. A recent study suggests that N95 respirators may significantly reduce the risk of exacerbations and hospitalisations during periods of severe air pollution, such as during wildfires [104]. The use of air cleaners (with high-efficiency particulate air (HEPA) and carbon filters) may also be effective in improving symptoms and reducing the risk of exacerbations in patients with COPD, who live in a home that has an indoor $PM_{2.5}$ content >10 $\mu g \cdot m^{-3}$. In a randomised controlled trial, Hansel *et al.* [105] showed that the use of air cleaners led to a >50% reduction in household $PM_{2.5}$ concentrations. Importantly, those who used an air cleaner in their homes were 70% less likely to experience a moderate exacerbation requiring the use of systemic corticosteroids or antibiotics than those in the sham control group with improved symptoms and less reliance on rescue inhalers [105]. These data suggest that air cleaners that can significantly reduce household exposure to $PM_{2.5}$ and other components of air pollution should be considered in COPD patients who are symptomatic and reside in homes with suboptimal air quality. Mitigation and management strategies are summarised in box 3.

Conclusions

There is a mounting body of evidence to link air pollution with COPD and exacerbations, although there is substantial variability in risk across patients. Single nucleotide polymorphisms in certain antioxidant genes and airway anatomy may account for individual susceptibility. More studies are needed as the problem of acute episodic increases in air pollutant concentrations may impact a considerably large proportion of the patients living with mild/moderate and even undiagnosed COPD. There is compelling evidence showing that reduction in air pollution leads to improvements in symptoms and lung function. Moreover, because many constituents of air pollution are also potent greenhouse gases, public strategies to lower air pollution

BOX 3 Mitigation strategies to improve the health of patients living with COPD exposed to high levels of air pollution

- Strong public health policies to reduce ambient air pollution (*e.g.* transition to solar, wind or hydropower; installation of efficient stoves and chimneys) [27]
- Public broadcast warnings and advisories when ambient pollution levels exceed acceptable minimal thresholds; personalisation of this information through the use of apps [108]
- Use of air cleaners for patients who live in homes with indoor $PM_{2.5}$ content >10 $\mu g \cdot m^{-3}$ [76]
- Consider use of N95 respirators during periods of severe air pollution (*e.g.* during wildfires) [104]

$PM_{2.5}$: particulate matter ⩽2.5 µm in diameter.

levels are likely to improve the health of communities and mitigate the adverse effects of climate change. Thus, the best preventive strategy is to institute policies to lower ambient air pollution levels. While these policies are implemented, more targeted actions can be recommended during poor air quality episodes, and patients living with COPD should avoid going outdoors and use indoor air cleaners (with HEPA and carbon filters) to reduce their overall exposure to air pollution particles.

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