Towards the elimination of chronic obstructive pulmonary disease: a *Lancet* Commission

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Executive summary

Despite substantial progress in reducing the global impact of many non-communicable diseases, including heart disease and cancer, morbidity and mortality due to chronic respiratory disease continues to increase. This increase is driven primarily by the growing burden of chronic obstructive pulmonary disease (COPD), and has occurred despite the identification of cigarette smoking as the major risk factor for the disease more than 50 years ago. Many factors have contributed to what must now be considered a public health emergency: failure to limit the sale and consumption of tobacco products, unchecked exposure to environmental pollutants across the life course, and the ageing of the global population (partly as a result of improved outcomes for other conditions). Additionally, despite the heterogeneity of COPD, diagnostic approaches have not changed in decades and rely almost exclusively on post-bronchodilator spirometry, which is insensitive for early pathological changes, underused, often misinterpreted, and not predictive of symptoms. Furthermore, guidelines recommend only simplistic disease classification strategies, resulting in the same therapeutic approach for patients with widely differing conditions that are almost certainly driven by variable pathophysiological mechanisms. And, compared with other diseases with similar or less morbidity and mortality, the investment of financial and intellectual resources from both the public and private sector to advance understanding of COPD, reduce exposure to known risks, and develop new therapeutics has been woefully inadequate.

In this *Lancet* Commission on COPD, our objective is to set the course to eliminate the disease by challenging accepted dogma and generating debate. We recognise that many of our recommendations could not be used as the foundation for evidenced-based guidelines. However, that is not our goal. We believe that a wholesale rethinking of COPD is needed. In general, we believe that the traditional incremental approach to advancing understanding of disease and developing new methods for diagnosis and treatment has failed. In particular, we advocate for: broader understanding of risk factors (including the devastating effects of global poverty) and the preventive measures necessary to avoid future cases of COPD, disruptive approaches to diagnosis that are not solely based on spirometric airflow limitation but also involve identification of early pathological changes that are more amenable to reversal, classification of the disease into

types that share pathophysiological similarities and could lead to novel preventive and therapeutic approaches, and a new approach to the diagnosis and assessment of exacerbations of COPD that focuses on disease mechanisms. We also advocate for a coordinated plan to combat the disease through increased financial investment, broad public policy initiatives, regulatory reform, and the alignment of health-care systems, which will enable a path towards prevention and cure rather than crisis management.

The most efficient way to reduce the burden of COPD is to ban cigarette smoking in all its forms. We strongly advocate for this ban, and support the associated financial, technological, and retraining investments that would be necessary to prevent economic disaster among people dependent on the tobacco industry for their livelihood. However, risk factors unrelated to tobacco are increasingly responsible for the burden of COPD, and are likely to surpass the risk attributable to smoking within the next two decades. These risks include many underappreciated factors that span the life course, from in-utero exposures to maternal factors leading to preterm birth or low birthweight, early-life infections, and indoor and outdoor pollution. Poverty increases the prevalence of these risk factors but decreases societal efforts to control them. Messaging targeted at medical professionals, government officials, private corporations, and the general public should emphasise these risk factors and drive preventive strategies. Otherwise the tobacco-related COPD crisis will be replaced by a COPD crisis driven by one or more of the other factors.

The definition of COPD requires the presence of spirometric airflow limitation, which all but eliminates the possibility that the disease could be cured or eliminated globally because the pathological changes required for airflow limitation are almost certainly permanent. We advocate for a broader definition of COPD that includes people with airflow limitation detected by more sensitive pulmonary function tests or pathological changes detected by imaging techniques. This broader definition will enable detection of patients with earlier pathological changes, which would enhance the possibility of understanding the mechanistic pathways driving disease inception and could thus lead to the development of effective treatments to interrupt and reverse the course of COPD. In low-income settings, we also advocate for the use of risks and symptoms to identify a population with probable COPD, in whom

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preventive measures and low risk non-pharmacological and pharmacological treatments could be beneficial. Throughout the Commission, we have provided similar options for alternative approaches when technology, the health-care system, or the personnel available limit the implementation of our recommendations.

Closely tied to the inadequacy of current diagnostic criteria is the failure to classify COPD in a way that could help to identify new approaches to prevention and treatment. We recommend that COPD be classified into types based on five main risk factors: genetics, early-life events, pulmonary infections, tobacco smoke exposure, and pollution. This approach mirrors that developed for pulmonary hypertension in the 1970s, which has revolutionised understanding of the disease and led to numerous novel therapeutics targeting individual classes of the disorder. We recognise that the risks factors leading to airflow limitation are numerous, and that many patients are affected by more than one. However, this is also true for patients with pulmonary hypertension, who can have more than one mechanism driving their disease (eg, heart failure and coexistent lung disease). Our proposal is not perfect and, like the WHO classification of pulmonary hypertension, will require iterative refinement, but it is far more likely to yield new therapeutics than a system that relies solely on the presence of spirometric airflow limitation and a patient's level of dyspnoea and exacerbation frequency (the extent of current attempts to classify COPD).

An acute worsening of COPD is termed an exacerbation, and such episodes account for a substantial proportion of the attributable cost of the disease and are associated with accelerated lung function loss, prolonged impairments in quality of life, and similar prognosis to many stage III or IV solid organ malignancies. Yet exacerbations tend to be imprecisely defined, and their severity is judged according to the site of treatment rather than the extent of underlying physiological derangement. Few exacerbations are thoroughly investigated to establish the underlying trigger (despite the availability of many diagnostic tools). Reflexive treatment with corticosteroids or antibiotics, or both, is prescribed in almost all cases—a therapeutic approach that has not changed in more than 30 years and in some cases is almost certainly harmful. We call for an objective definition of COPD exacerbations, a standardised assessment, and a precision approach to treatment (such a treatment approach will take time, because the development of new therapeutics will be contingent on the implementation of the new definition).

In the almost 4 years since this Commission was formed, the devastating COVID-19 pandemic has led to unprecedented efforts to align health authorities, regulatory agencies, private corporations, and the public in the fight against the disease. Although many parts of the world do not yet have access to the vaccines and treatments that were rapidly developed to combat COVID-19, the availability of these therapeutics in many high-income countries has shown that barriers preventing a coordinated response to a global crisis can be overcome and that a rapid response is possible. We argue that such a response is needed for the many chronic diseases that cause far greater yearly morbidity and mortality than COVID-19, including COPD. This response will require substantially increased investment in public health policies to prevent exposure to risk factors, implementation of our proposals to capture COPD earlier and enable phenotyping of patients, and research and development of precision therapeutics.

The ultimate objective of this *Lancet* Commission is to set the course to eliminate COPD, which will require novel and more effective approaches to preventing new cases and reversing the disease in people who are currently affected. We propose six core strategies to achieve this ambitious goal: (1) a broadened understanding of the multiple and interacting risk factors for COPD; (2) classification of the disease into types based on underlying causative mechanisms, including genetics, early-life events, respiratory infections, and tobacco and other environmental exposures; (3) implementation of a more inclusive diagnosis of COPD, allowing for the detection of mild disease before irreversible pathological changes have occurred; (4) development of personalised prevention and treatment strategies for both stable disease and exacerbations that are informed by a holistic assessment of COPD pathophysiology, symptoms, and patients' needs, capabilities, and preferences; (5) investment in the development of curative and regenerative therapies that go beyond the largely symptomatic treatment options available; and (6) deployment of public health preventive strategies for banning smoking and maintaining clean air. We are fully cognisant that the scientific evidence to support some of our proposals is lacking. However, it is the intention of the Commission to generate discourse and debate, catalyse momentum, and provide a much-needed new vision to set the course towards the elimination of COPD.

Introduction

The lungs are constantly exposed to environmental factors throughout life and are vulnerable to a range of insults including tobacco smoke, infections, and pollutants.[1] Even in utero, environmental exposures and maternal factors can increase the fetus's risk for respiratory disease later in life.[2] Tremendous progress has been made towards understanding the pathogenesis of chronic obstructive pulmonary disease (COPD) and risk factors for developing the disease (including non-tobacco-related factors). However, the prevalence of chronic respiratory disease—of which COPD is the most prevalent type—increased by almost 40% between 1990 and 2017, and by 2017 chronic respiratory disease had become the third leading cause of death globally.[3]

Key messages

- Chronic obstructive pulmonary disease (COPD) is a global health emergency that affects people from all countries, socioeconomic classes, and age groups, although it disproportionately affects poor and disadvantaged people.
- A substantial proportion of the COPD burden is preventable. Prohibiting all kinds of smoking and eliminating exposure to any form of air pollution would greatly reduce the burden of the disease.
- COPD is a complex and heterogeneous disease, and its pathophysiology implicates varying degrees of airway remodelling, inflammation, and tissue destruction. This heterogeneity manifests in the wide variations in respiratory symptoms, systemic consequences, and comorbid conditions among patients.
- Throughout the life course, there are multiple lung function trajectories, several of which can lead to COPD. Recognition of these varied trajectories, and the fact that not all patients develop COPD as a result of accelerated loss of lung function, could lead to new preventive and therapeutic approaches.
- COPD should be classified into five types on the basis of the predominant risk factor driving the disease: genetics, early-life events, respiratory infections, tobacco exposure, or other environmental exposures. Pathophysiological mechanisms related to each of these exposures could translate into distinct diagnostic, prognostic, and therapeutic considerations.
- Diagnosis should be based on expanded criteria including the presence of respiratory symptoms, personal history of risk factors, and persistent airflow limitation or ventilatory heterogeneity as assessed by spirometry, other pulmonary function testing, or CT. Airflow limitation based on spirometry alone is insufficient to diagnose COPD because spirometry does not reliably capture early airway changes or emphysematous destruction of the lung parenchyma, and probably only detects irreversible disease.
- Reducing the frequency of COPD exacerbations is a crucial step on the path towards the elimination of COPD. Diagnosis of exacerbation should be based on standardised assessments and should be confirmed by evidence of worsening airflow limitation or ventilatory heterogeneity, airway or systemic inflammation, or lung infection in a patient with increased respiratory symptoms (after exclusion of other disorders with similar presentations).
- The severity of a COPD exacerbations should be judged not in terms of the type of treatment or the setting in which care is provided, but rather based on objective categorisation of the degree of clinical, biological, and physiological deterioration. The Commission proposes the elimination of the definitions for mild or moderate exacerbations, such that exacerbations would be either severe or not severe.
- Current pharmacological and non-pharmacological therapies improve respiratory symptoms and quality of life, but are not available to many people with COPD. There is a moral imperative to improve access to effective treatment. Additionally, the development of curative and regenerative therapies for COPD is more likely to succeed if focused on early disease and pathophysiological differences underlying the specific disease types.
- Elimination of COPD requires consistent and coordinated action and substantially greater investment of financial and intellectual resources from all stakeholders, including medical professionals, governmental health and regulatory agencies, private industry, and the general public.

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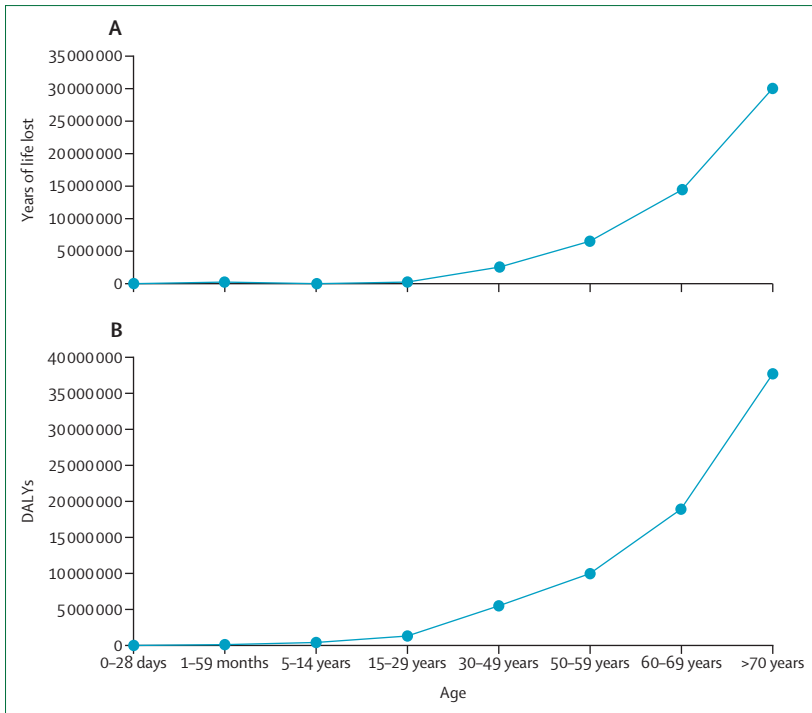mdransfield@uabmc.edu

COPD accounted for about 55% of all chronic respiratory diseases in both men and women in 2017, a relative increase of 5·9% since 1990.[3] Globally, COPD affects more than 300 million people and, in 2019, it resulted in 3·3 million deaths, ranking as the eighth leading cause of years of life lost. COPD is associated with an increase in disability-adjusted life years and years of life lost across the life course (figure 1). This substantial and increasing global burden makes COPD a public health problem that requires urgent attention.

COPD is a heterogeneous respiratory condition characterised by a combination of injury to, and remodelling of, the airways, lung parenchyma, and lung vasculature. These lung insults result in progressive airflow limitation, leading to increased dyspnoea, disability, and premature death.[5] Common symptoms of COPD include dyspnoea, chronic cough (often associated with phlegm), exercise intolerance, and episodic flare-ups of respiratory symptoms, which have been termed exacerbations.[6] The disease also causes substantial social and economic consequences for both individual patients and health systems. Limitations in normal daily activities due to COPD-related breathlessness—and the subsequent psychological implications for social life, family life, and overall quality of life, leading to fear, anxiety, and social isolation—are often underappreciated. COPD affects people from all countries, socioeconomic classes, and age groups, but the magnitude of its effects varies: elderly people and people in low-income and middle-income countries (LMICs), where 80% of COPD deaths occur, are disproportionately affected.[7]

As the prevalence of COPD has steadily increased, understanding of the disease has also advanced. Tobacco products are responsible for most of the disease burden worldwide, and their continued production and distribution is unconscionable. However, COPD can no longer be thought of solely as a self-inflicted disease caused by smoking. Rather, it is a complex condition caused by multiple risk factors that can interact and coexist throughout life—as evidenced by the fact that not

Figure 1: DALYs (A) and years of life lost (B) to COPD
In 2019, COPD was the seventh leading cause of DALYs globally and the eighth leading cause of years of life lost.[4] DALYs=disability-adjusted life-years. COPD=chronic obstructive pulmonary disease.

all smokers develop COPD and at least 20–30% of people with COPD have never smoked.[8] Indeed, it is very likely that a substantial proportion of COPD is preventable, and there is an opportunity to greatly reduce the burden of the disease through prompt, coordinated, and pragmatic efforts from the medical community, governmental bodies, and society as a whole.

COPD: a global health crisis

COPD has become a global health crisis partly as a result of the failure of governmental, medical, and scientific agencies, as well as private enterprises, to eliminate active cigarette smoking and to recognise and eliminate other environmental exposures. This Commission[9] aims to change the course of this global emergency by demanding urgent action targeting the factors most responsible for the uncontrolled burden of COPD. We will focus on the greatest difficulties to overcome, which lie in these key areas: (1) the effects of multiple overlapping risk factors, (2) scarce and insensitive diagnostic tools, (3) complex, unpredictable, and inadequate treatments, (4) disproportionate risk and financial burden in lower income populations, (5) misalignment and poor coordination of health-care systems, and (6) inadequate research funding (panel 1).

Multiple, overlapping, and interacting risk factors

Smoking is the main and most characterised cause of COPD, but other important and overlooked risk factors

include genetics, early-life events (including those occurring in utero), infections, and detrimental environmental exposures.[8,10] Premature births are associated with the development of COPD[11] and are increasing as a result of inadequate maternal and prenatal health care in low-income settings, advances in neonatal care (leading to improving survivorship among extremely preterm infants), changes in maternal age, and an increase in multiple births due to assisted reproductive technologies. In many parts of the world, prevalence of tuberculosis and HIV remain very high, and both are associated with airflow limitation. In addition, pneumonia accounts for more than 2 million deaths in children annually; survivors of pneumonic infections often do not attain maximum lung function as young adults, and thus are predisposed to COPD.[12] The increasing burden of COPD is also closely tied to environmental exposures in both industrial and non-industrial settings. Unfortunately, legislation passed to limit environmental exposures, as well as efforts to ban or restrict the use of cigarettes and other inhaled substances, have not been sufficient or adequately enforced. Despite the establishment in 1983 of the Energy Sector Management Assistance Program, a global knowledge and technical assistance programme that aimed to mitigate household cooking exposures and improve clean energy access, more than 40% of the world's population is still exposed to high levels of indoor air pollution.[13] This pollution results from the use of biomass fuels in inefficient and poorly ventilated stoves for cooking and heating in low-income countries, and from the use of gas for cooking and heating without extractor fans in middle-income and high-income countries. Occupational exposures to dusts, gases, and fumes are also a major risk factor for COPD and are common in many industries, including manufacturing, mining, steelworks, farming, and automotive repair.[14] In some occupations, respiratory protection standards are inadequate and poorly enforced and there is often a dangerous lag between the identification of harmful exposures and implementation of protective measures. Absurdly, some legislation allows employers to assess the risks, set the standards for safe levels of airborne pollutants, and enact protective measures without any external regulatory oversight.[15]

Insensitive diagnostic tools, delayed recognition, and late presentation

COPD is currently defined as incompletely reversible limitation of expiratory airflow (as detected by spirometry) due to a combination of small airway remodelling and emphysematous destruction of the lung parenchyma.[5,16] It is underdiagnosed and typically diagnosed late, partly because it results from accumulated damage to the respiratory system over the life course. Spirometry forms the foundation of diagnosis of COPD. The presence of spirometric expiratory airflow limitation as defined by a ratio of the forced expiratory volume in 1 s (FEV_1) to

the forced vital capacity (FVC) of less than 0·7 (or less than the adjusted lower limit of normal) is the gold standard. This approach to disease detection has facilitated communication in the medical community and empowered epidemiological investigation and development of symptomatic treatments, but it provides an overly simplified view of COPD. Spirometry is a poor predictor of symptoms, exercise capacity, and overall quality of life and does not capture the heterogeneity of the disease.[17] Moreover, the emphasis on spirometric obstruction precludes detection of very early disease, which might be more amenable to interception—or even reversal and cure—and has led to therapies that primarily target moderate-to-severe disease. It is misleading to equate the absence of spirometric expiratory airflow limitation to the absence of COPD, because airway and parenchymal changes are clearly present in many individuals with normal spirometry results.[18] In addition, even people with compromised and worsening lung health but surplus functional reserve might have unremarkable spirometric results compared with the population-based norm, with thresholds for disease crossed only after irreversible pathological changes have occurred in the lung.[19] COPD can also sometimes arise early in life due to the failure of normal lung development (usually, lung function peaks around age 25 years in men and age 18–20 years in women).[20] These patients are rarely if ever assessed for respiratory disease and seldom undergo spirometry, and better biomarkers are needed to identify them.

Definition of COPD based on spirometric criteria alone is flawed and dangerous because early airway changes and emphysematous destruction of the lung parenchyma do not reliably translate to airflow limitation as measured by spirometry. This erroneous notion increasingly hinders progress and is partly responsible for the lack of biomarker-based assessments to signal early compromise in lung health.[19] Additionally, there is often a delay in diagnosis of COPD until the lung damage is irreversible because of the under-recognition of respiratory symptoms and the fact that prolonged periods of disease activity and worsening lung health can be associated with no or only minimal symptoms (figure 2).

Furthermore, despite the years-long emphasis on the crucial role of spirometry in the diagnosis of COPD, this simple technology is still not universally available, much less routinely used worldwide (figure 3, table 1). Global attempts to define COPD preceding the development of spirometric airflow limitation, including the concept of pre-COPD,[21] have raised awareness of the complexity of the problem but have not yet translated to improved diagnosis or outcomes. A new approach to diagnosis will require both consideration of the predictive utility of respiratory symptoms alone[22] and expansion of diagnostic criteria based on non-spirometric lung function assessments and imaging. In a survey that we did through the European Respiratory Society, we found that

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Panel 1: Challenges in the prevention and cure of chronic obstructive pulmonary disease

- Multiple, overlapping, and interacting risk factors for disease
  - Genetics
  - Early-life events
  - Respiratory infections
  - Inhalation of tobacco, drugs, and other combustible substances
  - Environmental exposures (eg, indoor pollutants, ambient air pollution, occupational exposures)
- Insensitive diagnostic tools, delayed recognition, and late presentation
  - Dependence on spirometry, which is unsuitable for the detection of mild disease
  - Poor availability of other diagnostic tools
- Insufficient or inefficient treatment options
  - No curative treatments
  - Inadequate disease control in most patients
  - Unpredictable treatment responses and complex treatment delivery
- Disproportionate burden among poor and disadvantaged people
  - Increased prevalence of risk factors for compromising lung health
  - Unequal social and financial burdens
  - Limited access to treatment in low-income and middle-income countries
- Misalignment of health-care system
  - Scarcity of multidisciplinary and specialist care
  - Mixed availability of, and support for, smoking cessation and pulmonary rehabilitation
- Lack of innovation in management and inadequate research funding

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chest CT was as available as or more available than spirometry in many countries (figure 3, table 1).

These challenges highlight the need to seek alternative methods with increased sensitivity that can detect the pathological processes associated with COPD at an early stage. Diagnostic methods that show lung destruction or airway remodelling either directly (eg, CT) or indirectly (eg, by showing reductions in gas exchange [diffusion capacity] or impaired respiratory mechanics [forced oscillation]) should be considered as complementary to spirometry.

Insufficient treatment options

In addition to inadequate diagnostics, treatment of COPD is suboptimal for several reasons. The most prominent therapeutic shortcoming is the absence of curative therapies. Furthermore, available pharmacological treatments largely target symptoms (and often have only limited effects, including on cough and sputum production), and none reverse the underlying
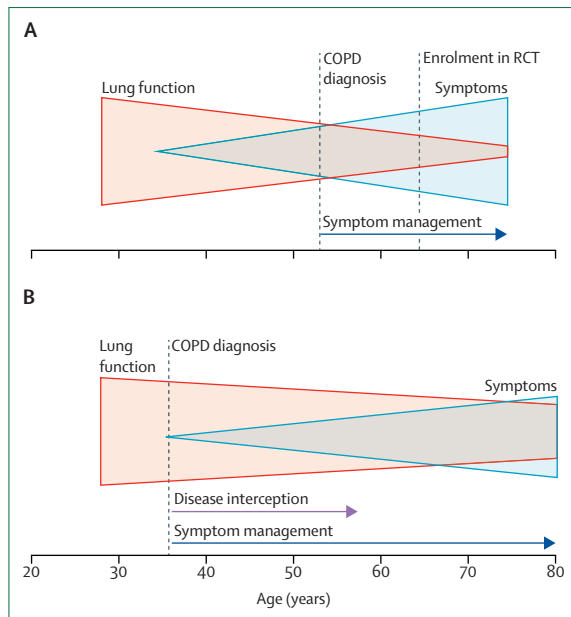
Figure 2: The importance of early diagnosis to eliminate COPD
(A) Currently, COPD is diagnosed at a stage when pathological changes are irreversible. This late diagnosis is due to a combination of factors, including the lack of predictive biomarkers, under-recognised clinical symptoms, a long period of disease activity associated with no or minimal symptoms, and reliance on spirometry, an insensitive diagnostic tool. (B) Implementation of a more inclusive diagnosis of COPD allows for the detection of early disease before irreversible pathological changes have occurred and could lead to disease interception. COPD=chronic obstructive pulmonary disease. RCT=randomised controlled trial.

airway remodelling, emphysema, and vascular abnormalities characteristic of the disease. We should not settle for this state of affairs, and rather should strive for treatments that halt, reverse, and cure the disease. However, such therapies will require dedicated and substantial research investment commensurate with the scope of the problem. The type of approach necessary is exemplified by the development of CFTR modulators that successfully target the underlying molecular defect driving cystic fibrosis and have revolutionised treatment of that disease (although we argue that the price of CFTR modulators should be lowered to increase net health benefits to society). Although the genetics of COPD are far more complicated than those of cystic fibrosis, which means that ground-breaking treatments will almost certainly be more difficult to identify, the goal should still be to reverse pathology and normalise physiology.

Few markers reliably predict responsiveness to available COPD treatments. Circulating blood biomarkers such as C-reactive protein and procalcitonin are associated with response to antibiotic therapy at the time of exacerbations.[23] Blood eosinophil counts seem related to response to inhaled corticosteroids in stable disease and could predict response to systemic corticosteroids during exacerbations.[24,25] However, although other blood-based and radiological biomarkers

have been suggested, few have proven clinically useful and there is an urgent need for novel, robust predictors of therapeutic response and adverse effects. In other chronic and progressive diseases, the identification of meaningful surrogate and intermediate endpoints—eg, glucose and glycated haemoglobin in diabetes, cholesterol in ischaemic heart disease—has been instrumental in controlling morbidity and mortality. Such biomarkers can be used to identify early disease and measure responsiveness to treatment when there is still time to delay, prevent, or reverse organ damage.

Furthermore, lung function impairment, respiratory symptoms, and exacerbations (and the associated morbidity, mortality and health-care costs) are only partly mitigated by available treatments. Typically, the degree of improvement in these outcomes in randomised trials is 15–25% irrespective of the therapy tested.[26] The heterogeneity of COPD, combined with the fact that many trials enrol patients based only on the presence of spirometric obstruction, means that the potential benefits of treatments suitable for only a subgroup of patients can be overlooked. This situation could be avoided if greater phenotypic or endotypic characterisation were used to define more homogeneous populations whose disease was driven by the specific pathway targeted by the drug under investigation. The development of monoclonal antibodies aimed at specific underlying biological mechanisms has led to substantial reductions in symptoms and exacerbations (and associated hospital admissions) in some subsets of patients with severe refractory asthma.[27] This precision approach has been widely discussed but infrequently tested in patients with COPD.

COPD is associated with numerous systemic manifestations and comorbidities, and thus symptoms can reflect not only the extent of lung function impairment but also the effects of deconditioning, obesity, anaemia, anxiety, depression, and congestive heart failure, among other disorders. As a consequence, the classification of patients with COPD solely according to respiratory symptoms could lead to overestimation of the severity of pulmonary disease—and thus of the potential benefit of bronchodilators and inhaled corticosteroids—and underestimation of the effect of managing related conditions via different treatment approaches. Because of shared risks factors, including ageing and tobacco smoking, and perhaps also shared pathobiology, the proportion of patients with COPD who also have multimorbidity is higher than that of patients with many other chronic diseases; thus a multi-dimensional and patient-centred approach to prevention, diagnosis, and treatment is required.[28]

Non-adherence or incorrect administration of inhaled medications is common in COPD because of the number and complexity of delivery devices, a problem that is not shared with most other chronic conditions.[29] Devices include dry powder inhalers, pressurised
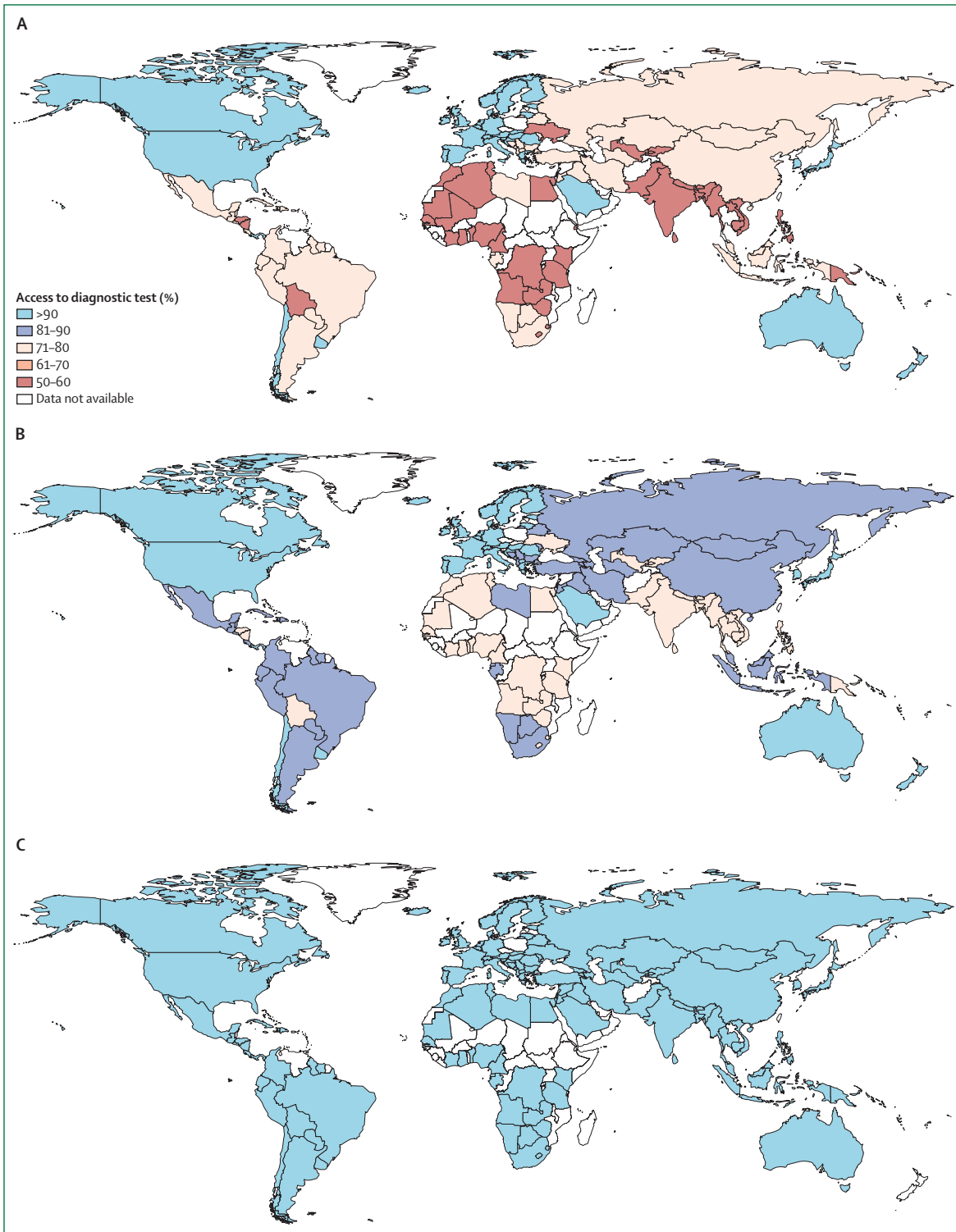
***Figure 3*: Proportion of global population with access to spirometry (A), chest CT (B), and chest radiography (C) for diagnosis of chronic obstructive pulmonary disease**
Data were obtained from the survey done by the Commission (appendix pp 1–5).

See **Online** for appendix

	Primary and specialist care	Primary care only	Specialist care only	Limited* availability in primary or specialist care, or both	Not available
Lower-middle-income countries (n=11)					
Spirometry	2 (18%)	0	4 (36%)	5 (45%)	0
Reversibility testing	1 (9%)	0	6 (55%)	4 (36%)	0
Whole body plethysmography	0	0	3 (27%)	5 (45%)	3 (27%)
Diffusion capacity measurement	0	0	3 (27%)	5 (45%)	3 (27%)
Arterial blood gas analysis	0	0	6 (55%)	5 (45%)	0
Chest radiography	6 (55%)	3 (27%)	0	2 (18%)	0
Chest CT	1 (9%)	0	7 (64%)	3 (27%)	0
Upper-middle-income countries (n=15)					
Spirometry	3 (20%)	2 (13%)	6 (40%)	4 (27%)	0
Reversibility testing	2 (13%)	1 (7%)	8 (53%)	4 (27%)	0
Whole body plethysmography	0	0	5 (33%)	9 (60%)	1 (7%)
Diffusion capacity measurement	0	0	6 (40%)	8 (53%)	1 (7%)
Arterial blood gas analysis	1 (7%)	2 (13%)	8 (53%)	4 (27%)	0
Chest radiography	8 (53%)	4 (27%)	3 (20%)	0	0
Chest CT	3 (20%)	0	10 (67%)	2 (13%)	0
High-income countries (n=17)					
Spirometry	12 (71%)	1 (6%)	3 (18%)	1 (6%)	0
Reversibility testing	8 (47%)	0	9 (53%)	0	0
Whole body plethysmography	0	0	16 (94%)	1 (6%)	0
Diffusion capacity measurement	1 (6%)	0	14 (82%)	2 (12%)	0
Arterial blood gas analysis	1 (6%)	0	15 (88%)	1 (6%)	0
Chest radiography	12 (71%)	0	4 (24%)	1 (6%)	0
Chest CT	4 (24%)	0	12 (71%)	1 (6%)	0

Data are n (%). We sent an online survey to more than 100 national and regional respiratory societies worldwide, including the American Thoracic Society, European Respiratory Society, the Pan African Thoracic Society, and the Asociación Latinoamericana de Tórax. We received responses from societies representing 43 of the 120 countries approached. Countries were categorised into the four World Bank income groups based on the 2019 gross national income per person. The lower-middle-income countries that responded were Algeria, India, Kenya, Kyrgyzstan, Moldova, Nepal, Pakistan, Philippines, Sri Lanka, Tunisia, and Viet Nam. The upper-middle-income countries were Albania, Brazil, Bulgaria, Costa Rica, Iran, Jordan, Kazakhstan, Lebanon, Malaysia, Mexico, North Macedonia, Serbia, South Africa, Thailand, and Türkiye. The high-income countries were Australia, Austria, Belgium, Canada, Finland, France, Germany, Lithuania, Norway, Poland, Portugal, Slovenia, Spain, Switzerland, Taiwan, Uruguay, and the USA. No surveys were returned from physicians in low-income countries (see appendix for additional methods).
*The availability of a diagnostic test was defined as "limited" if it was available to a maximum of 15% of patients.

Table 1: **Availability of tests considered relevant in the diagnosis of chronic obstructive pulmonary disease, by country income group**

metred-dose inhalers, and soft mist inhalers, each of which requires different inhalation techniques that are often not taught to patients (or are taught incorrectly). Determinants of poor inhaler technique include older age and the number of devices used, both of which become more problematic as the disease progresses.[30]

Monitoring of treatment responses is often challenging, particularly in patients who do not exhibit early sympto-matic clinical responses. It takes time to establish whether exacerbation frequency improves with initial or modified treatment, and such improvements might not be perceived by patients or reliably detected by health-care providers. Increases in lung function are more easily identified, but are not always accompanied by clinically relevant improve-ments in patient-reported outcomes or reduced

exacebation risk. Similar patterns are apparent for the effects of pulmonary rehabilitation in COPD: effects on exercise capacity and symptoms during daily activities differ both between and within patients over time. Treatment responses would be best monitored according to composite outcome measures, but these are complex, time consuming, and difficult to administer.

Disproportionate effects on marginalised populations
Almost all risk factors for COPD are associated with low socioeconomic status, which also predicts poor clinical outcomes. These disparities are most pronounced when LMICs are compared with high-income countries, but are also a major cause for concern within high-income countries, where poverty and neighbourhood-level socio-economic disadvantage are independent predictors of COPD and associated respiratory morbidity.[31] Further-more, individual-level and neighbourhood-level socio-economic factors partly explain racial health disparities in COPD,[32] probably through clustering of risk factors such as tobacco smoking, poor indoor and outdoor air quality, substandard housing, and limited access to healthy food and health care.

As discussed previously, premature birth is a risk factor for COPD.[33] Global data from 2017 showed that less than two-thirds of pregnant women received the recommended four or more antenatal visits and nearly 20% of women had no health insurance before pregnancy, both of which increase the risk for premature birth.[34] Household air pollution is associated with an increased risk of COPD. More than 2·4 billion people, generally among the world's poorest, are estimated to rely directly upon biomass fuel for their heating and cooking needs.[35] Tobacco smoking is also increasing in LMICs (although it is declining in high-income countries), partly because there is little or no regulation of tobacco sales and partly because of the dependence of farmers on the tobacco industry for their livelihood.

In 2019, an estimated 1·1 billion people smoked worldwide.[36] Although various legislative and social measures decreased the number of cigarette smokers globally by approximately 60 million between 2000 and 2018, population growth eliminated any overall benefit associated with this decline.[36] Tobacco companies have also begun to produce alternatives to cigarettes, including electronic nicotine delivery systems, such as vaping devices and e-cigarettes. Aggressive and unregulated marketing of these devices is directed at young and vulnerable people and is highly successful, as evidenced by the substantially increased prevalence of smoking in children and the fact that the initial age of smoking onset is lower than ever before.[37]

The worldwide economic burden of COPD is high, not only because of the disease's prevalence, chronic course, and high treatment costs, but also because of the high costs of informal caregivers, productivity loss due to premature withdrawal from the workforce, and increased

absenteeism due to illness. For obvious reasons, poor, disadvantaged, and vulnerable people are particularly affected by these factors.

Limited access to therapeutics results in suboptimal care and is of particular concern in LMICs. An online survey done by the Commission through national respiratory societies in 43 countries showed that the availability of pharmacological and non-pharmacological interventions was highly variable (figure 4; appendix pp 1–5). Access to advanced treatments such as endobronchial valves, lung volume reduction surgery, and lung transplantation was restricted even in many high-income countries, and there was almost no access in LMICs. More concerning was the very low availability of standard inhaled treatments for COPD in LMICs. Our survey suggested that access to pharmacotherapy was also affected by out-of-pocket costs: 50% of patients in low-income and lower-middle-income countries, and 33% of those in upper-middle-income countries, were unable to afford COPD pharmacotherapies.

Shortcomings of health-care systems

The financial challenges of COPD care are amplified by the complexity and poor coordination of many health-care systems and the misalignment between reimbursement for components of care and their relative efficacy. In many countries, most patients with COPD are managed in primary care because there are few incentives to seek specialist input and a shortage of pulmonologists. Care needs to be provided by clinicians who have sufficient training: pulmonologists or chest physicians or primary care practitioners who have interest, training, and expertise in COPD and updated knowledge of the treatments and procedures necessary for optimal care. In high-income countries, people with severe COPD commonly see specialists and the substantial proportion of patients with multimorbidity tend to see many health-care providers.[28,38] Unfortunately, coordination of care and communication between these providers is often poor and systems are prone to inefficiencies such as duplication of tests and services, late recognition of progression and acute events, and overtreatment and undertreatment; patients are also at risk of the potentially harmful effects of drug interactions due to polypharmacy.[39] In addition, decisions about management are based on guidelines that are informed by clinical studies done in populations that do not represent the general COPD population. For many patients, even those in high-income countries with good overall access to health care, the system tends to be fragmented and difficult to navigate.

In most countries, health-care systems react to acute illnesses and are reimbursed well for those efforts, but little support is available for the prevention of chronic diseases. This is perhaps best illustrated by the failure to deliver low-cost, effective smoking cessation treatments
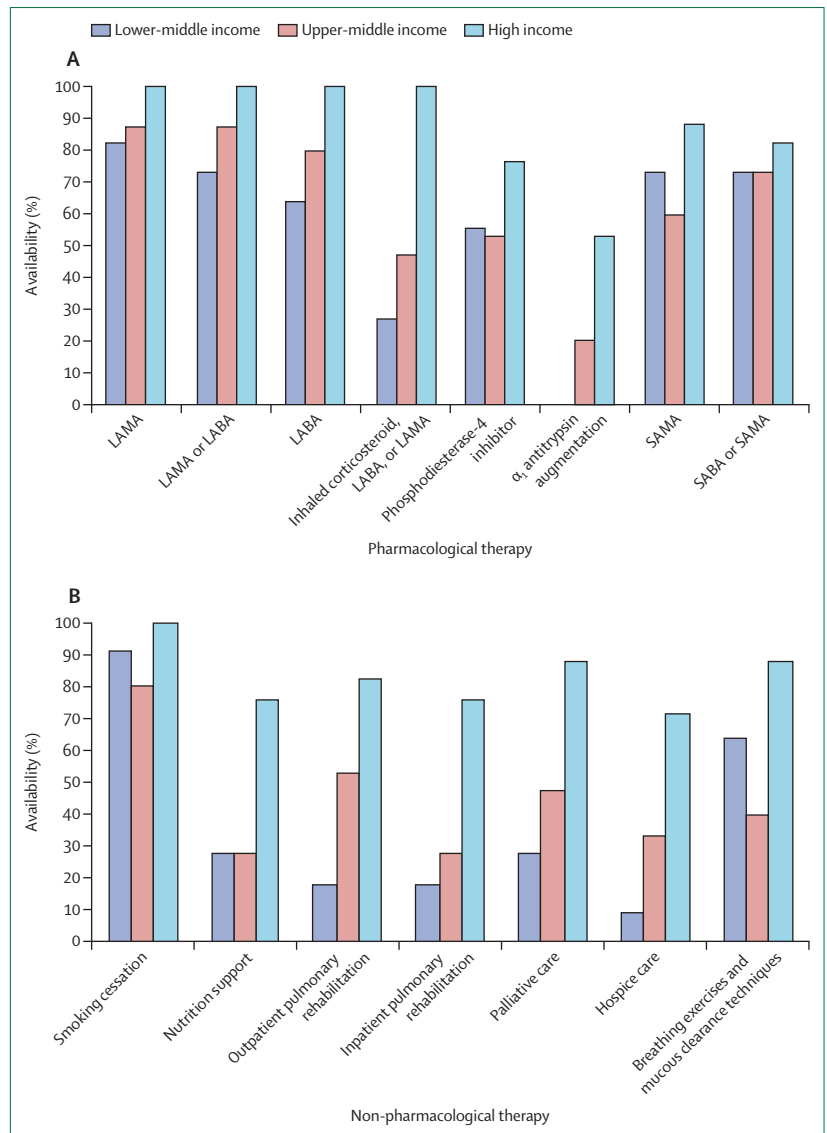

Figure 4: **Availability of pharmacological therapies (A) and non-pharmacological therapies (B) for chronic obstructive pulmonary disease in lower-middle-income, upper-middle-income, and high-income countries** LAMA=long-acting muscarinic antagonist. LABA=long-acting β agonist. SAMA=short-acting muscarinic antagonist. SABA=short-acting β agonist.

or interventions to reduce residential biomass fuel exposure in low-income countries. The costs of care associated with smoking account for about 15% of the aggregate health-care expenditure in high-income countries and are estimated to be US$500 billion worldwide.[40] In 2018, the US Medicaid programme covered the cost of smoking cessation treatments in only 15 states—and in only two states were all barriers to patient access removed, including requirements for co-payment, previous authorisation and counselling for the medication, limited treatment duration, and limited numbers of quit attempts per year and per lifetime.[41] Most countries in Europe, the Western Pacific, and southeast Asia offer nicotine replacement therapy or

some cessation services, or both, but the costs tend to be covered for only one type of therapy (and are sometimes only partly covered).[42]

Lack of innovation and inadequate research funding

Over the past 25 years, there have been few innovations in either pharmacological or non-pharmacological management of COPD, and the disease lags far beyond other conditions with high morbidity and mortality in terms of the development of precision medicine approaches. The pharmacological innovations that have reached the market are primarily long-acting, dual and triple combinations of well-established inhaled bronchodilators and corticosteroids. Furthermore, the use of digital information technologies to identify early COPD or COPD exacerbations, or to support remote monitoring and self-management, is not widespread. Multiple factors, including a lack of investment and resources in the studies necessary to generate the evidence for these approaches, structural barriers to embedding digital tools, and the older age and lower socioeconomic background of the COPD population, are implicated in the scarcity of these approaches.

Furthermore, there is substantial misalignment between the burden of COPD and the priority afforded to the disease by governmental and other funding agencies. Similar to the low resources dedicated to smoking cessation, the US National Institutes of Health's funding for COPD-specific research is low compared with that for other chronic diseases, such as cardiovascular disease, cancer, and diabetes (figure 5).[43,44] COPD research is also substantially underfunded compared with asthma: asthma received $338 million in funding from the National Institutes of Health in 2020 ($81,500 per US death) whereas COPD received $121 million (less than $800 per US death). The reasons for this discrepancy are complex and difficult to rationalise. Possible explanations include the substantial social stigma that inaccurately characterises COPD as a self-inflicted disease, which is less evident in cardiovascular disease and type 2 diabetes, even though lifestyle factors are important contributors to both illnesses. There has been substantial recent research investment in lung cancer, for which smoking is the most important risk factor, for the development of biologics and immunotherapies, which in many cases offer only an incremental survival advantage. This survival advantage is accepted by regulators as sufficient proof of benefit and thus incentivises investment from the pharmaceutical industry. For a chronic disease such as COPD, incremental or overall survival advantages are far more difficult to show because of the prolonged trajectory of the illness.

In addition to hampering diagnosis and causing confusion about the goals of COPD treatment, over-reliance on spirometry has also complicated drug development. Despite knowledge that FEV_1 correlates poorly with individual patient-centred outcomes such as dyspnoea, risk of exacerbation, and mortality, regulatory bodies continue to emphasise FEV_1 as the primary outcome by which to assess novel treatments.[45] FEV_1 is also an inadequate surrogate marker for many key COPD features because it correlates only weakly (if at all) with morphological and imaging endpoints such as emphysema and small airways disease.[46] Regulatory bodies have been slow to accept patient-reported outcomes as primary endpoints in registration trials in favour of spirometric measures. Neither exercise tolerance tests, which are approved in other respiratory disorders, nor emphysema assessment by CT, which is arguably more reproducible in clinical trial settings than spirometry, have been approved as endpoints for COPD. New therapies that reduce emphysema progression could plausibly have little effect on FEV_1 but substantial value in altering the disease course. However, the regulatory environment renders the risk of testing these potential therapies prohibitive. Ultimately, what matters to patients are quality of life and survival; all other endpoints are surrogates. The US Food and Drug Administration
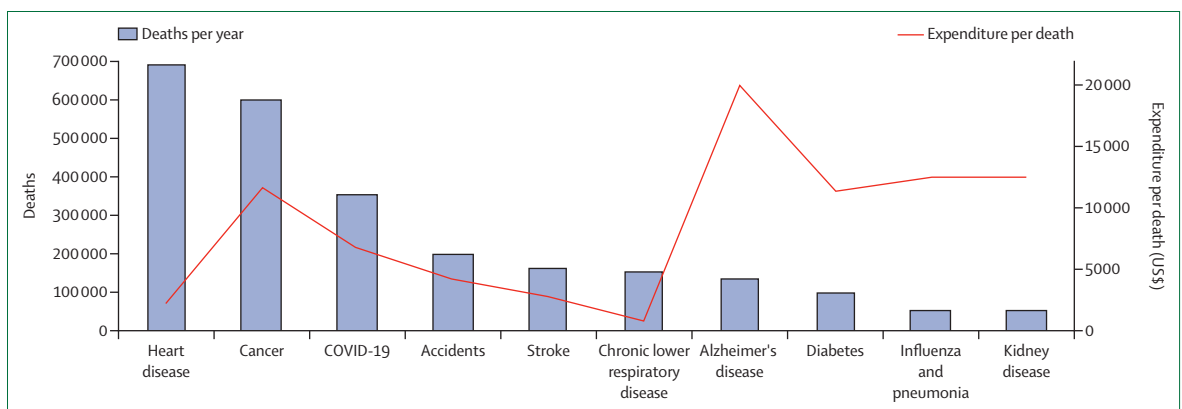

Figure 5: **Research expenditure per death by the US National Institutes of Health, by disease, 2020**
The bars depict the deaths per year per disease in the USA. In terms of US dollars committed per death from each disease, chronic obstructive pulmonary disease receives the lowest funding.[43,44]

articulates this concept by requiring endpoints in therapeutic trials to measure how a patient feels, functions, and survives. FEV_1 does not qualify based on this criterion and is at best a weak and imperfect surrogate.

Under the current regulatory standards, studies large enough to show reductions in mortality are expensive, although some such studies have been done.[47,48] However, these studies have enrolled heterogeneous patient populations solely according to spirometric criteria and perceived exacerbation risk and not on the basis of the underlying pathophysiology driving the disease. Therefore, it is not surprising that until 2018, mortality advantages for inhaled therapies were difficult to show.[47,48] Furthermore, instruments that have been validated in COPD suggest that therapies such as bronchodilators and inhaled corticosteroids have only moderate effects on quality of life, despite the detectable effects of these treatments on FEV_1 and exacerbations.[47,48]

As a multidisciplinary group of Commissioners, we have a unique opportunity to present ideas that can reframe the problems facing the field and challenge accepted dogma that could be hampering progress. We hope to foster discussion and debate, advocate for policy change, and influence the research agenda to steer the global COPD community and its stakeholders towards a path that leads to COPD elimination. The objective of the *Lancet* Commission on COPD is to identify the factors contributing to the unrelenting burden of the disease and to propose actionable recommendations to transform our approach to prevention, management, and research.

COPD: beyond tobacco smoking

Real-world observations call into question Fletcher and Peto's traditional conceptual definition of COPD as a self-inflicted disease caused by tobacco smoking that is associated with accelerated loss of lung function and eventually results in persistent respiratory symptoms.[49] This definition, which was formulated in 1976, has increasingly been undermined by evidence of risk factors for COPD other than smoking.[8] These risk factors can have distinct pathophysiological mechanisms and clinical manifestations, which can in turn affect diagnosis and treatment. Not all smokers develop COPD and not all patients with COPD smoke or exhibit accelerated decline in lung function with age.[50] In fact, about half of patients with COPD seem to have a normal rate of lung function decline, but never reached the expected healthy peak of lung function in early adulthood.[20] There is mounting evidence that other factors, such as genetic predisposition, in-utero events and prematurity, early-life events, early or recurrent respiratory infections, and exposure to air pollution and biomass fuel smoke, account for a large proportion of COPD cases worldwide.[51] Respiratory morbidity in early childhood can affect respiratory morbidity in late adulthood. Early-life events can alter the respiratory and immune system in ways that
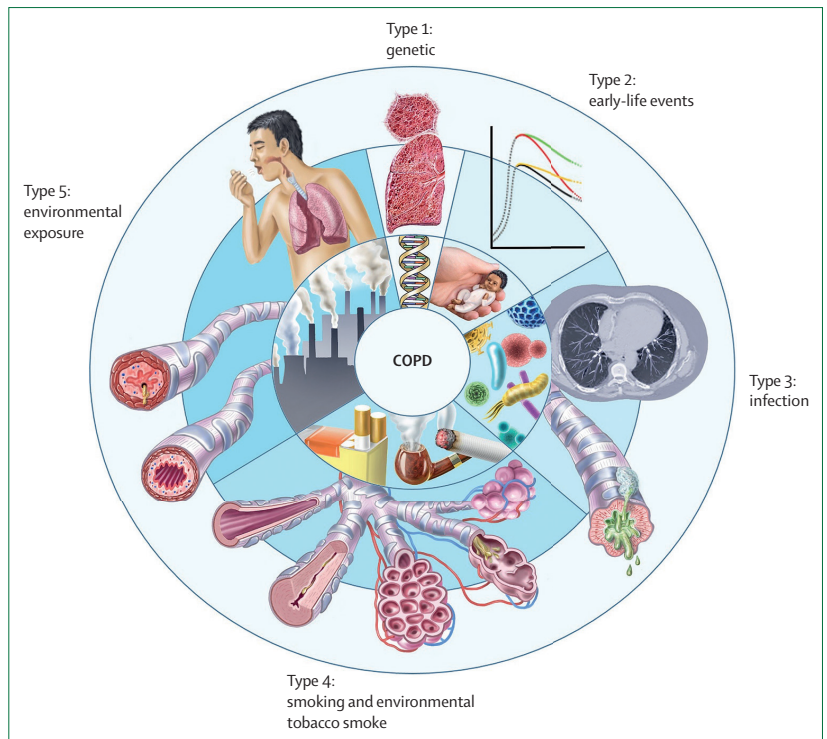

Figure 6: Proposed classification of COPD according to major risk factors
The five proposed types are related to genetics, early-life events, infections, exposure to tobacco smoke, and environmental exposures. We remain cognisant, however, that individuals are prone to multiple exposures throughout life, which could cause additive or interactive damage to lung health. COPD=chronic obstructive pulmonary disease.

render the lungs more vulnerable, leading to greater susceptibility to adult risk factors—eg, maternal smoking accentuates the effects of later-in-life smoking and occupational exposures in the infant, heightening the risk of airflow limitation.[52,53]

Although the clinical consequences of disease caused by these other risk factors might be similar to that of tobacco smoke exposure, peculiarities in the pathophysiological mechanisms related to each of these exposures could plausibly translate into distinct diagnostic, prognostic, and therapeutic considerations. Non-smoking patients with COPD tend to be younger and have better lung function than patients who develop COPD secondary to smoking.[54] More in-depth investigation into these COPD subtypes is essential to advance precision COPD management. With this in mind, we propose a novel COPD classification. This approach defines five types that capture the variation in the causes of COPD and in turn link to the underlying molecular endotypes driving pathophysiology (figure 6). Although we acknowledge that there are unmodifiable risk factors for COPD and potentially new risk factors that have yet to be identified, many COPD cases (and the associated disease burden) are preventable. To prevent new cases of COPD and ultimately eliminate the disease, it is necessary to heighten awareness of the non-tobacco

risk factors while still acknowledging the terrible toll of tobacco smoking. We propose a model that challenges accepted dogma. We concede that some aspects of our proposal are speculative. However, disruptive efforts to reclassify diseases have been successful in the past. For example, the 1975 classification of pulmonary hypertension was initially controversial, but the resulting WHO system has since led to substantial progress in understanding of the disease.[55] Pulmonary hypertension has not been eliminated, and the 1975 classification system has required substantial refinement over the years, but the model has still been instrumental in improving identification of people affected by the disease and in focusing research efforts that have yielded life-prolonging therapeutics. The optimal approach to diagnose and classify COPD is uncertain, but the status quo is not working. Given that most COPD is preventable, development of a system that prioritises risk factors will hopefully set a course towards elimination.

Type 1: genetically determined COPD

Genome-wide association studies focusing on disease phenotypes defined by spirometry suggest that the genetic heritability of COPD is moderate.[56] Although about 40% of the variability in airflow limitation and up to 60% of the risk for COPD related to smoking is attributable to genetics,[57] α_1 antitrypsin deficiency and telomerase reverse transcriptase mutation are the only two monogenetic variants that have been clearly shown to have a causative role in the disease. The role of epigenetic changes resulting from gene–environment interactions, such as DNA methylation and histone modifications, which could influence the development of COPD in adulthood, is incompletely explored.[56,58] In addition, smoking behaviour could have genetic origins.[59]

α_1 antitrypsin deficiency

α_1 antitrypsin is a glycoprotein mainly produced in hepatocytes that inhibits neutrophil elastase and thus protects the lungs from the neutrophil-elastase-mediated development of emphysema. Deficiencies in α_1 antitrypsin are noted in 1–2% of white patients with COPD.[60] The most frequently observed abnormal genotype is *PI*ZZ*, which is also associated with more severe disease than other genotypes, including the *PI*S* allele. Homozygosity for *PI*ZZ* is associated with the development of COPD irrespective of smoking status, whereas heterozygosity is associated with a moderate deficiency of α_1 antitrypsin that increases the risk of developing COPD in smokers (figure 7). Current guidelines recommend that all patients with COPD be tested for α_1 antitrypsin deficiency.[5] This guideline has become even more pertinent since the publication of data showing the cumulative effect of multiple α_1 antitrypsin (*SERPINA1*) variants on lung function.[61]

Patients with α_1 antitrypsin deficiency are similar to patients with COPD in that they are prone to dyspnoea, chronic and episodic bronchitis, and upper respiratory tract infections (URTIs), although they might present at a younger age than people with COPD that is unrelated to α_1 antitrypsin deficiency.[60] The rate of decline of FEV_1 in α_1 antitrypsin deficiency is associated with smoking and environmental exposures, male sex, age, FEV_1 at diagnosis, the presence of chronic bronchitis, and bronchodilator responsiveness. Although the emphysema distribution patterns and airway changes are broadly similar between α_1 antitrypsin deficiency-related COPD and COPD unrelated to α_1 antitrypsin deficiency, patients with α_1 antitrypsin deficiency tend to have greater basilar emphysema.[62] The proportion of patients experiencing exacerbations of COPD is similar between α_1 antitrypsin deficiency and non-α_1 antitrypsin deficiency populations.

TERT mutations

Telomerase enzymes protect against telomere shortening during every cell division, but lose activity as people age.[63] Mutations in telomerase genes result in increased telomere shortening, stem-cell exhaustion, premature ageing, cell senescence, and increased secretion of pro-inflammatory cytokines from the senescent cells.[64] The resulting chronic inflammatory state leads to lung tissue destruction and remodelling. Although these pathophysiological changes become more common with age even without mutations in *TERT* (the gene that encodes for telomerase reverse transcriptase), mutations can exaggerate these processes and are predominantly found in women and in 1% of patients with severe early-onset COPD.[65–67] The same *TERT* mutation can result in differing patterns of lung damage according to the environment, leading to fibrosis in non-smokers and emphysema in smokers.[68]

Type 2: COPD related to early-life events
Prematurity

Around 10–12% of all deliveries are premature births,[69] resulting in approximately 15 million premature infants worldwide yearly, some born as early as 23 or 24 weeks' gestation. Prematurity is associated with low birth-weight, nutritional problems, susceptibility to respiratory infections, and poor lung function early in life. Together with insults such as exposure to tobacco smoke in the second half of pregnancy, prematurity can cause substantial impairment in alveolar, vascular, and airway development, leading to reduced lung maturation postnatally, particularly in infants born before 28 weeks' gestation.[70] These pathological changes increase susceptibility to COPD later in life—thus, prevention of prematurity is key to the elimination of COPD.

Respiratory failure is the most common morbidity associated with extremely preterm birth. As a result of advancements in neonatal and perinatal care, infant survival is higher than ever before. Chronic lung disease of infancy can occur together with prematurity and be worsened by other risk factors, such as neonatal

infection, persistent ductus arteriosus, and fluid overload. The production of free radical species from supplemental oxygen, together with barotrauma and pressure from mechanical ventilation, induces additional lung injury and scarring. Chronic lung disease of infancy is characterised by lung fibrosis, emphysema due to poorly developed alveolar spaces, disturbed vascular growth with pulmonary hypertension and vascular hyperreactivity, airflow limitation, and bronchial hyper-responsiveness.

Severe lung injury associated with prematurity can also result in the clinically well recognised bronchopulmonary dysplasia.[71] The term bronchopulmonary dysplasia is often used interchangeably with chronic lung disease of prematurity. The American Thoracic Society guidelines suggest that chronic lung disease of infancy is the final common pathway of a heterogeneous group of pulmonary disorders that start in the neonatal period and include both bronchopulmonary dysplasia and chronic lung disease of prematurity.[72] We are not suggesting that bronchopulmonary dysplasia should be considered a subtype of COPD. Rather, we are noting that pulmonary insults during the prenatal and early-life periods lead to lower peak lung function in adulthood, which in turn contributes to the development of COPD in some individuals.[2,73]

Lung function anomalies due to prematurity persist through childhood[73] and into adulthood, with clear associations between prematurity and airflow limitation in the early thirties and early fifties.[74,75] Long-term CT studies also show that the lungs of people born prematurely who have chronic lung disease (particularly those born during the pre-surfactant period) have many pathological similarities to those of people with COPD.[11,76]

Although there are gradual improvements in indices used as surrogates for quantifying lung function, most individuals born prematurely with low birthweight or who are small for gestational age never attain age-appropriate levels of pulmonary function and are at increased risk of persistent airflow limitation and COPD later in life.[74,77] Air pollution exposure during pregnancy can also affect postnatal lung function in preterm infants more severely than infants born at term.[78]

Childhood asthma

Asthma is the most frequently diagnosed chronic airway inflammatory disorder in childhood. Whether asthma is a single disease or encompasses several diseases as an umbrella term is arguable. Whether early-life asthma is a cause or consequence of poor lung development is debatable because a child with abnormal lung development due to any of the mechanisms discussed previously is likely to have symptoms that mimic those of asthma. Therefore, it is quite likely that such a child would end up being diagnosed with, and treated for, asthma. Conversely, longitudinal observations suggest that some early-life
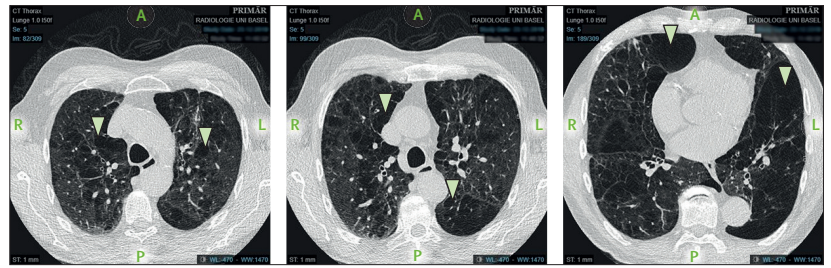

***Figure 7:* Thoracic CT of a 72-year-old patient with α₁ antitrypsin deficiency**
The arrows show emphysematous areas in the lung. The patient is an ex-smoker with a 40-pack-year history of tobacco use, a COPD assessment test score of 21 (range 0–40; higher scores suggest greater disease effects), and a modified medical research council dyspnoea score of 3 (0–4; higher scores suggest greater dyspnoea). COPD=chronic obstructive pulmonary disease.

wheeze phenotypes slow the growth of adolescent lung function.[79] Furthermore, early-life asthma adversely affects later lung function independent of early-life lung function.[80]

Together, these findings suggest that, at minimum, a diagnosis of early-life asthma has an adverse effect on lung development. Evidence that early-life asthma is associated with airway remodelling also supports this notion.[81] Teasing out the relative contributions of early-life risk profiles from childhood lung function in the development of poor adult lung function and COPD is highly complex. However, Bui and colleagues[80] reported that the effect of childhood asthma on development of COPD and risk of low lung function in middle age is largely transmitted through active adult asthma (and to a lesser degree through reduced childhood lung function), highlighting the importance of controlling asthma throughout life. Overall, the balance of evidence suggests that controlling early-life asthma could be crucial to the prevention of COPD, although definitive data for the beneficial effects of asthma control on long-term lung function, especially in relation to incidence of COPD, are not available.[82]

Type 3: infection-related COPD

Pulmonary and systemic infections are among the most important non-smoking related risk factors for chronic lung disease and COPD, especially in LMICs.[4,7,8] An estimated 10–42% of people with early-life pneumonia, tuberculosis, or HIV develop COPD.[83–85]

Childhood infections

Multiple factors influence childhood respiratory health, but respiratory infections are of particular concern. Respiratory syncytial virus is one of the best-described pathogens causing pneumonia and other lower respiratory tract infections (LRTIs).[86] Impaired lung function at birth, which is influenced by maternal nutrition,[87] pre-pregnancy body-mass index (BMI),[88] and maternal smoking, could predispose to LRTIs. Estimates suggest that childhood LRTIs account for 33% of COPD in non-smokers.[54] Frequent LRTIs in the first seven years of life are associated with pulmonary vasculature abnormalities, airway remodelling, parenchymal destruction, and impairment in
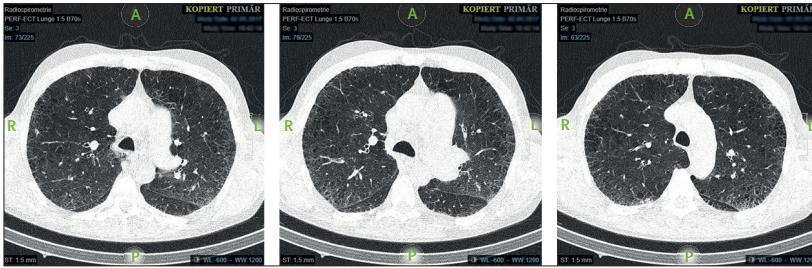
Figure 8: **Thoracic CT of a patient aged 56 years diagnosed with HIV in 1995**
At the time of the CT, the patient was an active smoker and had a diffusing capacity of the lungs for carbon monoxide of 32·2% of predicted, severe pulmonary hypertension, and cachexia (body-mass index 18·9 kg/m²).

	Childhood infections	Tuberculosis	HIV
Hypertrophy of airway smooth muscle	Sometimes occurs normally, but can be mildly important	Moderately important	Mildly important
Thickening of basement membrane	Sometimes occurs normally, but can be mildly or moderately important	Very important	Mildly important
Inflammation*	Mildly to moderately important	Moderately important	Mildly important
Change in turnover of extracellular matrix	Moderately important	Very important	Moderately important
Damage to mucociliary clearance or mucus hypersecretion	Moderately important	Moderately important	Moderately important

*Neutrophilic, eosinophilic, or paucigranulocytic inflammation.

Table 2: **Importance of pathophysiological features associated with infection-related causes of chronic obstructive pulmonary disease**

mucociliary clearance and local immune defences.[89] Impaired airway host defences create an environment that is susceptible to both viral and bacterial infection and chronic colonisation of the lower respiratory tract.[90] Chronic colonisation can induce a chronic inflammatory response, with bacterial antigens causing hypersensitivity that enhances airway hyperreactivity and lung damage.

Tuberculosis-associated COPD

Tuberculosis remains a major health problem in many countries. There is a strong association between a history of tuberculosis and the development of COPD in non-smoking patients.[91] Despite successful treatment of tuberculosis, impaired lung function often persists.[92] The risk of airflow limitation in patients with a history of tuberculosis is more than twice that in patients with no history of tuberculosis. The chronic inflammatory response and long-term tuberculosis-associated structural alterations, such as airway remodelling with scar formation, stenosis, and bronchiectasis, are the pathological basis for the development of COPD. Patients with tuberculosis-related COPD have higher air trapping, more fibrosis and emphysema, and an altered immunological and inflammatory profile (fewer neutrophils) compared with patients with COPD with no history of tuberculosis.[93] Lung parenchymal inflammation in tuberculosis is mediated heavily by matrix metalloproteinases, which have a substantial role in the accelerated destruction of the pulmonary extracellular matrix noted in COPD.[93]

HIV-associated COPD

During the first decade of the AIDS epidemic, opportunistic infections were the most common reason for pulmonary impairment in patients with HIV. However, despite limitations in their methods, cross-sectional studies report a prevalence of emphysema as high as 65% in people with HIV, which is in turn associated with early mortality.[94] Other features, including airflow limitation, diffusion impairment, and pulmonary vascular abnormalities, are also present to varying degrees. The advent of highly active antiretroviral therapy resulted in an improvement in HIV outcomes, but increased respiratory symptoms and decreased lung function have been noted in people with HIV and are independent of other risk factors such as smoking and intravenous drug use.[95] In people with HIV, the prevalence of COPD can be as high as 23%, and people with HIV and COPD experience more rapid declines in lung function than HIV-negative people with COPD.[96] Age, BMI, and CD4 cell count are independently associated with HIV-related COPD[97] and impaired diffusing capacity of the lungs for carbon monoxide (DLCO) is also highly prevalent in patients with HIV (figure 8). COPD, like other chronic illnesses, is underdiagnosed in patients with HIV and the implications of this underdiagnosis are incompletely recognised and understood.[94]

Emerging data suggest that the pathological changes present in infection-related causes of COPD are highly variable (table 2). This variability suggests the possibility that the underlying molecular pathways driving COPD could also be different, which in turn has implications for treatment and cure.

Type 4: COPD related to smoking or vaping

The clinical and radiographic characteristics associated with tobacco smoking are well known and account for most knowledge about COPD. Maternal smoking, second-hand and third-hand smoking (ie, exposure to pollutants that settle on surfaces when tobacco is smoked indoors), and vaping or e-cigarette smoking also have substantial implications for lifelong lung health.

In-utero and early-life exposure to tobacco smoke

Smoking during pregnancy is associated with serious adverse outcomes, including preterm birth, low birthweight, birth defects, and infant death.[98] In 2016, roughly 7·2% of mothers in the US smoked during pregnancy; the greatest prevalence of smoking was in mothers aged 20–24 years (10·7%).[98] Long-lasting

respiratory impairment is evident in children of mothers who smoked during pregnancy, and these effects can be amplified in offspring who also smoke as adults: reduced lung function at birth limits the ability to reach healthy peak lung function, and tobacco smoke then triggers early and accelerated lung function decline.[2] Maternal smoking during pregnancy is also associated with increased respiratory symptoms, including wheezing and chronic bronchitis.[99] Notably, a study[100] has suggested that exposure to smoking among parents even before conception—especially paternal exposure to smoke around puberty—can affect lung function in offspring.

Infants whose mothers smoke during the prenatal and postnatal periods have thicker large-airway walls than infants born to non-smokers, and this increased wall thickness has been associated with sudden infant death syndrome.[101] Among children in grades 4 (average age 10 years), 7 (average age 13 years), and 10 (average age 16 years), a history of in-utero exposure to tobacco smoke was associated with reduced forced expiratory flow and peak expiratory flow rate.[102] Airflow limitation in offspring exposed to maternal smoke could be due to reduced alveolarisation and augmented lung damage as a result of increased oxidative stress from nicotine exposure.[103] Glutathione S-transferase genes have a crucial role in managing oxidative stress in the lungs. A study[104] of US children aged 6–10 years showed an association between maternal smoking and reduced lung function, which was more common in children whose mothers were carriers of a *GSTM1* deletion (and thus had no functional enzyme). An Australian study[105] also showed that carriers of null mutations in glutathione S-transferase genes and *GSTP1* genes with Ile/Ile alleles have an increased likelihood of developing lung function deficits by early-to-late adolescence when exposed to tobacco smoke in early life.

Animal models have also shed light on the adverse respiratory effects of prenatal and early-life exposure to smoke. Neonatal mice exposed to cigarette smoke over 4 days had increased neutrophils and macrophages in bronchial fluid and displayed increased mucus production, goblet cell hyperplasia, and evidence of epithelial and vascular remodelling.[106] Offspring of rhesus monkeys exposed to nicotine during their pregnancy had increased airway resistance, increased collagen deposition, decreased lung weight, and fixed lung volumes compared with offspring whose mothers were not exposed to nicotine.[107]

Passive smoking
The EU-funded TackSHS project concluded that the respiratory burden attributable to second-hand smoke exposure is still substantial and mainly due to exposure in the home.[108] Around 1·5% of deaths in children aged 0–14 years and 0·6% of deaths in non-smoking adults are attributable to exposure to second-hand smoke at home.[107] Exposure to second-hand smoke as an adult in the workplace is also associated with increased respiratory symptoms, including cough, phlegm, and frequent colds.[109]

Similar to the effects of active smoking, passive smoking can contribute to increased airway inflammation and mucus secretion.[110] Independent of their current smoking status, adults whose mothers smoked during their childhood had lower FEV_1 and higher risk of post-bronchodilator airflow limitation than those who were not exposed to smoke by their mothers during childhood.[53] Maternal smoking during early childhood could also have an additive effect on the negative consequences of the individual smoking habits of offspring, particularly airflow limitation.[111] The radiographic changes noted in COPD are also evident in adults with and without COPD who have a history of exposure to environmental tobacco smoke in childhood.[112]

Vaping or e-cigarette use
Use of e-cigarettes impairs the body's ability to fight infections by reducing the antimicrobial activity of alveolar macrophages, neutrophils, and epithelial cells and by reducing the expression of immune-related genes.[113] Use of e-cigarettes alters more than 200 proteins in airway epithelial cells; the effects on 113 of these proteins are unique to e-cigarette use.[114]

E-cigarette use can promote lung inflammation and is associated with respiratory symptoms such as cough, sputum production, and wheezing.[115] In an analysis[116] in which combustible tobacco use was controlled for, e-cigarette use was independently associated with chronic respiratory diseases, including asthma and COPD. The risk of developing COPD from combustible cigarettes is doubled when combined with e-cigarette use, and use of e-cigarettes in never-tobacco-smokers doubles or triples the risk of self-reported COPD, emphysema, or chronic bronchitis.[117] Additional studies are needed to confirm the direct effect of e-cigarettes on the development of COPD, but the available data are compelling and concerning.

Cannabis
The prevalence of cannabis smoking is rapidly increasing. In Canada, for instance, where cannabis use was legalised in 2018, 27% of the population surveyed reported having used cannabis in 2020, an increase of 25% from 2019.[118] Only 17% of cannabis smokers also regularly consume tobacco cigarettes, and the remainder never or almost never smoked both tobacco and cannabis.[118] Although the respiratory health effects of cannabis smoking are incompletely understood, emerging evidence suggests probable harm. A 2018 systematic review[119] showed that cannabis use was associated with increased risk for cough (risk ratio [RR] 2·0), sputum production (3·8), wheezing (2·8),

and dyspnoea (1·6) compared with not using cannabis or tobacco. The effect of cannabis smoking on lung function and particularly on lung function decline over time is controversial. In the largest study[120] of its kind, the Canadian Cohort of Obstructive Lung Disease followed up 1285 participants aged 65 years for an average of 6 years. The findings suggested that heavy cannabis use (defined as more than 20 joint-years [the number of joints per day, multiplied by years]) was associated with a steeper decline in FEV$_1$ compared with non-smokers (–40·20 mL per year vs –10·75 mL per year; p=0·0007). The effects of cannabis on a molecular and cellular level are poorly understood. Endobronchial biopsies have shown that cannabis smokers have a greater degree of squamous metaplasia, goblet cell hyperplasia, and cellular disorganisation than non-smokers, at rates similar to those among tobacco smokers; the alveolar macrophages of cannabis smokers also show diminished phagocytic and antimicrobial activity.[121,122]

Type 5: environmental exposure-related COPD

Environmental exposure encompasses exposure to particles and gases from indoor fuel use, wildfire smoke, air pollution or smog, and occupational exposure. Emerging data suggest that different environmental exposures can lead to differing pathological processes leading to COPD (table 3).

Exposure to indoor pollutants

Roughly 3 billion people, mainly in LMICs, use biomass fuel for cooking and heating.[123] Particulate matter generated by inefficient and poorly ventilated stoves burning wood, crop waste, dung, or coal is a major source of indoor pollution. The World Bank estimated that the COVID-19 pandemic would push between 88 and 115 million people into extreme poverty, which could mean increased use of biomass fuels (as a result of being unable to afford more expensive alternatives).[124] Exposure to smoke from biomass fuels and other indoor air pollutants results in altered lung function, increased respiratory infections, and pronounced airway inflammation, all of which increase the risk of COPD.[125,126] COPD caused by biomass fuel smoke could have distinct features and demographic characteristics compared with that associated with tobacco smoking. COPD induced by exposure to biomass fuel pollution is more likely to affect older women born in rural areas and is associated with a higher prevalence of chronic bronchitis and bronchial hyperreactivity and milder airflow limitation and slower declines in lung function than cigarette smoke-induced COPD.[125,126] Exposure to biomass smoke leads to an airway-

	Indoor pollutant exposure	Ambient air pollution or smog	Wildfire smoke	Occupational exposure
Clinical manifestations				
Chronic cough	Moderately important	Moderately important	Moderately important	Very important
Sputum production	Moderately important	Moderately important	Mildly important	Moderately important
Dyspnoea	Moderately important	Mildly important	..	Moderately important
Wheezing	Mildly important	Mildly important	..	Moderately important
Exacerbations	Moderately important	Moderately important	Moderately important	Moderately important
Systemic manifestations	Moderately important	Mildly important	..	Mildly important
Airway remodelling and inflammation				
Hypertrophy of airway smooth hypertrophy	Very important	..	..	Very important
Thickening of basement membrane	Moderately important	..	..	Moderately important
Eosinophilic inflammation	Moderately important	..	..	Moderately important
Neutrophilic inflammation	Mildly important	Mildly important	Mildly important	..
Pauci immune inflammation	Mildly important	..	..	..
Change in turnover of extracellular matrix	Moderately important	..	..	..
Persistent airflow limitation				
FEV$_1$/FVC <0·70	Very important	Moderately important	..	Very important
Ratio of total to effective resistance	Very important	..	..	Very important
Difference in oscillation resistance at 5 Hz and 19 Hz	Very important	Moderately important	..	Very important
Reactance area	Very important	Moderately important	..	Very important
Parenchymal destruction				
CT emphysema	Mildly important	Mildly important	..	Moderately important
Decreased DLCO	Mildly important	..	..	Moderately important

FEV$_1$=forced expiratory volume in 1 s. FVC=forced vital capacity. DLCO=diffusing capacity of the lungs for carbon monoxide.

Table 3: Importance of pathophysiological features associated with environmental exposure-related causes of chronic obstructive pulmonary disease

predominant COPD phenotype with increased anthracosis, airway thickening, air trapping, small airway fibrosis, and pulmonary arteriole intimal thickening and less emphysema and goblet cell hyperplasia compared with COPD associated with tobacco smoking.[127] Evidence also suggests that exposures to indoor pollutants—even to concentrations lower than the WHO recommended limits—can lead to reduced lung function, particularly when the exposure occurs during early life.[128]

Ambient air pollution and smog

Globally, the population exposed to air pollution levels above the WHO Air Quality Guideline safe limit declined modestly between 2010 and 2016; however, this decline was driven by improvements in North America and Europe, whereas levels in Asia remain extremely high.[129] New WHO global air quality guidelines provide clear evidence of the damage that air pollution inflicts on human health at even lower concentrations than previously thought.[130] Exposure to low-to-moderate environmental air pollution during pregnancy and in the first two years of life is associated with decreased lung function after birth[131] and up to the sixth year of life.[132] Importantly, exposure to ambient pollution up to the sixth year of life was associated with reduced lung function not only in cross-sectional studies but also in longitudinal studies, in which children exposed to air pollution had a lower rate of lung growth than those not exposed to pollution.[133] Yet in the USA, roughly one in every 11 community schools lies within 150 m of a highway, truck route, or other road with substantial traffic.[134] Air pollution also has adverse effects in adults: the SAPALDIA study showed that living within 20 m of a main street increased the risk of sputum production and wheezing in never smokers.[135] Exposure to ambient air pollutants, particularly ozone and particulate matter, decreases FVC and FEV_1, increases respiratory symptoms, and increases the risk of emphysema in adults, irrespective of smoking status.[135]

Wildfire smoke

As a result of the hotter and drier conditions resulting from climate change, the number of wildfires has decreased but the intensity of the fires and the acreage destroyed have increased.[136] Smoke from wildfires is formed from a mixture of carbon monoxide, benzene, aldehydes, and polycyclic aromatic hydrocarbons.[137] A study[138] in the USA between 2004 and 2009 showed that racial and ethnic minorities older than 65 years and those living in poverty were particularly susceptible to developing lung disease from the air particulates in wildfire smoke. Increased respiratory symptoms and physician visits have also been reported in children exposed to the southern California wildfires during 2003.[139] Human airway epithelial cells exposed to wildfire smoke extract in vitro showed greater inhibition of autophagy and increased barrier dysfunction compared with cells exposed to cigarette smoke.[140]

Occupational exposures

Studies have suggested that occupational exposures to vapours, gases, dusts, or fumes are associated with the development of COPD[3] and emphysema and airway disease as measured by quantitative CT.[141] Such exposure occurs in a broad range of occupations, including—but not limited to—production plant workers, woodworkers, hairdressers, food service workers, and construction workers. A meta-analysis[142] showed that people occupationally exposed to airborne pollutants have a 22% increased risk of COPD and that 15% of all COPD cases in high-income countries are attributed to occupational exposures. Dust exposure from other occupations including cement, primary coffee processing, street sweeping, and quarry mines can also lead to decreased lung function and increased respiratory symptoms, especially cough and sputum production.

Why revisit the diagnostic criteria for COPD?

It is well accepted that COPD is a complex and heterogeneous disease: complex in that the disease has several distinct components and is driven by both genetic and environmental factors that dynamically interact over time, heterogeneous in that all components are not present in all individuals at any given timepoint and can vary in severity over time.[143] Diagnostic criteria for COPD capture none of this complexity nor the variation in underlying pathophysiology. Rather, they rely exclusively on the presence of spirometric airflow limitation in at-risk patients, as assessed by the post-bronchodilator ratio of FEV_1 to FVC. Unfortunately, spirometric airflow limitation is detectable only at later pathophysiological stages after the expression of genetic effects, early-life events, infections, and exposure to tobacco smoke or environmental factors have led to major damage to the lung. Thus the spirometric definition of COPD misses early pathological changes, which means that COPD is almost always diagnosed in patients with largely irreversible lung damage. Expansion of diagnostic criteria to encompass COPD heterogeneity will increase sensitivity for early disease and could lead to the discovery of new preventive measures and therapeutic approaches.

Varied pulmonary and extra-pulmonary COPD manifestations

The heterogeneity of COPD is shown by the substantial variation in respiratory symptoms and morbidity and the range of systemic consequences of the disease (and its common comorbid conditions). Dyspnoea upon modest exertion and chronic cough have been extensively explored in smokers with spirometrically defined COPD because they greatly affect patients and are typically the reason for seeking medical attention (although they are only weakly related to measures of lung function).[144] Challenges arise when clinicians see patients with no

respiratory symptoms but with airflow limitation, or vice versa. Although the importance of respiratory symptoms is generally acknowledged, which symptoms to consider or how severe symptoms should be before they are considered pathological remains unclear.

Acute respiratory exacerbations are common in patients with COPD but also occur in individuals with spirometrically normal lung function.[18] Characterised by increased cough, sputum production, and breathlessness, exacerbations are an important cause of accelerated decline in spirometric lung function, absence from work, hospital admissions, and mortality.[5] As we will discuss later in this Commission, the definition of an exacerbation is imprecise, which makes clustering of patients based on the predilection to exacerbations or the frequency of exacerbations challenging. Yet guidelines[5] use the term "frequent exacerbator" to define a group of COPD patients who experience at least two exacerbations per year and to define treatment for these patients. These patients have a worse prognosis than patients with fewer exacerbations, but the phenotype is not stable. Reducing the frequency of exacerbations is paramount, but permanent classification of patients according to an outcome of illness is counterproductive, because treatment could improve or prevent the outcome and thus change the patient's phenotype. As Lopez-Campos and colleagues have stated, "a clinical phenotype should be a natural manifestation of the disease and the phenotypic feature should be stable over time".[145]

The presence and severity of pulmonary hypertension in patients with COPD are also highly variable. In a study[146] in which CT and clinical features were used to identify airway remodelling and emphysema associated with COPD-related pulmonary hypertension, pulmonary hypertension was present in 34–57% of patients. No differences in age, dyspnoea, and or degree of emphysema or spirometric lung function measurements were noted between COPD patients with and without pulmonary hypertension. Patients with COPD and moderate pulmonary hypertension, however, had a shorter 6-min walk distance and lower oxygen partial pressure than those without pulmonary hypertension. Significant differences in airway remodelling and pulmonary artery diameter were also noted between patients with COPD with and without pulmonary hypertension, as measured by CT.

Cardiovascular, musculoskeletal, and mental disorders and diabetes are the most prevalent comorbidities among patients with COPD. The associations between these comorbidities or systemic manifestations and COPD can be classified into three clusters with different clinical, functional, and prognostic consequences. First, some conditions share risk factors and pathological pathways with COPD, including ageing, senescence, and exposures. This link is best exemplified by the fact that smoking is the primary risk factor for both lung cancer and COPD. Second, some chronic comorbidities

aggravate COPD, causing further deterioration or intensification of symptoms—eg, depression or cardiovascular disease can lead to reduced physical activity, weight-gain, and decreased lung function. Finally, some acute illnesses that require treatment can cause adverse effects on respiratory symptoms or pulmonary function.

Cardiovascular effects associated with COPD are not limited to the pulmonary vasculature. Patients with COPD have more cardiovascular disease than current and former smokers without COPD.[147,148] This increased burden of disease could be because of shared pathophysiology, such as increased oxidative stress, systemic inflammation, hypoxia, and physical inactivity.[148] Cardiovascular disease worsens the prognosis of COPD because it is implicated in the pathogenesis of exacerbations, and vice versa.[149] Indeed, most patients with mild-to-moderate COPD die of cardiovascular disease, not of respiratory failure.[150] It would be sensible to explore the extent to which the treatment of comorbidities affects COPD control and clinical outcomes, but such studies have not yet been done.

In addition to vascular effects, COPD is associated with other debilitating systemic manifestations such as cachexia and muscle dysfunction (eg, muscle weakness, sarcopenia). Cachexia is defined by the Cachexia Consensus Working Group as a complex metabolic syndrome that is associated with underlying illness and characterised by muscle loss.[151] It is diagnosed on the basis of weight loss of at least 5% in 12 months or less in the presence of an underlying disease, plus three of decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (increased C-reactive protein or interleukin 6, anaemia, or low serum albumin). Because of the challenges in obtaining this detailed information, the pragmatic diagnosis of cachexia in patients with COPD has been simplified to unintentional weight loss of greater than 5% in 6 months and a fat-free mass index less than 17 kg/m^2 in men and less than 15 kg/m^2 in women.[152] The prevalence of cachexia in patients with COPD attending outpatient clinics ranges between 4·6% and 10·4%, depending on the definition used; cachexia is associated with decreased FEV$_1$ and exercise capacity, more exacerbations per year, and increased mortality, irrespective of the definition used.[152]

Depression and anxiety in COPD are under-recognised and undertreated. Many patients experience anxiety or depression, and a bidirectional relationship between COPD and mental disorders is probably operational: individuals with mental disorders are more likely to smoke, which increases the risk of developing COPD, and the social isolation and disability associated with COPD can contribute to new-onset depressive symptoms. Additionally, mental comorbidities influence self-management strategies. Depression might be more strongly associated with patient-reported outcomes in

COPD than FEV_1.[153] Although depression in patients with COPD has been associated with low treatment compliance, poor quality of life, extended hospital stays, increased hospital admissions, and increased mortality, it is often untreated or incorrectly treated.[154]

Type 2 diabetes is a strong predictor of mortality in COPD and affects 16% of patients.[155] Several features associated with COPD have been identified as risk factors for type 2 diabetes, including physical inactivity and bodyweight. Use of inhaled corticosteroids in COPD increases the risk of new-onset type 2 diabetes and worsens glycaemic control.[156] Furthermore, low-grade systemic inflammation in COPD has been associated with altered glucose metabolism and the development of insulin resistance.[157]

Like COPD, lung cancer is primarily caused by smoking tobacco. In 2020, more than 2·2 million people were diagnosed with lung cancer.[158] COPD increases the risk of developing lung cancer, even in never-smokers.[159] The landmark National Lung Screening Trial[160] found that low-dose CT screening reduced mortality from lung cancer by 20%. In 2013, the US Preventive Services Task Force recommended yearly screening for current smokers and for people aged 50–80 years who had quit in the past 15 years and had at least a 30-pack-year smoking history. However, uptake of lung cancer screening in high-risk individuals in the USA (including those with COPD) remains low, particularly among poor and uninsured people.[161] Adoption of lung cancer screening practices is also low in LMICs because of lack of infrastructure, costs, social disparities, and cultural barriers.[162] Screening in COPD is complicated by the fact that although the risk of lung cancer increases as FEV_1 declines, the potential for curative treatment is reduced. In addition, patients with COPD are at increased risk of complications related to invasive diagnostic procedures.[163] However, an analysis[164] of the National Lung Screening Trial suggested a mortality advantage for those with mild to moderate airflow limitation, but not those with severe or very severe disease.

Varied lung function trajectories

There are various lung function trajectories throughout life, and more than one of these trajectories could lead to COPD. Recognition of these trajectories and the fact that not all patients develop COPD on the basis of accelerated loss of lung function could help to identify new preventive and therapeutic approaches. These variable lung function trajectories are due to the differential effects of multiple individual and environmental factors that influence lung function growth, peak lung function attained, duration of the plateau phase, and the subsequent rate of lung function decline.[2] Experimental identification depends on the frequency of lung function measurements, total duration of follow-up, and the number of participants in the study. To date, epidemiological evidence suggests that most lung function changes over the life course can be grouped into six major trajectories, resulting from lifelong, dynamic, or cumulative gene–environment interactions: persistently high lung function, average lung function, below average but stable lung function, persistently low lung function, below average lung function in early life followed by accelerated decline, and low lung function in early life followed by accelerated growth and average decline (figure 9).[165] Importantly, some children who initially follow the low lung function trajectory can regain normal lung function.[165] Understanding the mechanisms underlying this trajectory is essential to the discovery of therapeutic interventions that can potentially reverse or cure the disease.

The long-term presence of low lung function before a clinical diagnosis of COPD (which generally does not occur until patients are in their 50s or 60s) presents an opportunity to identify high-risk individuals at a time (eg, infancy, adolescence, early adulthood) when interventions could reduce risk of developing the disease. Early detection of people at risk and targeted prevention strategies are important to slow and perhaps arrest the development of COPD. Importantly, patients who develop COPD subsequent to different lung function trajectories could have different underlying pathological mechanisms, which could in turn lead to different clinical presentations, prognosis, and treatment needs. A study[20] showed that a similar proportion of people with normal peak lung function followed by an accelerated decline in FEV_1 developed COPD to those with low peak lung function and a normal decline in FEV_1. It seems highly unlikely that the pathological processes underlying these two trajectories are the same. However, a disadvantage of using lung function trajectories to define heterogeneity in COPD is that this approach is completely dependent on spirometry, which is rarely done in young people. Identification of novel biomarkers that distinguish the various lung function trajectories in the early decades of life is thus essential.

Patients have been characterised with early COPD on the basis of their age and a post-bronchodilator ratio of FEV_1 to FVC of less than 0·70.[21] This diagnostic approach does not consider early lung changes or account for symptomatic patients with normal spirometry. Some evidence suggests the potential importance of preserved ratio impaired spirometry, which is defined as reduced FEV_1 with a preserved FEV_1 to FVC ratio.[166] Use of the term pre-COPD has also been suggested.[21] Progress based on these classifications will be hindered by the tremendous heterogeneity of the patients included, partly because those with differing risk factors and underlying pathological processes are grouped together. Our suggestion for classification based on five COPD types, which admittedly can overlap, and new diagnostic criteria for these types, acknowledges the concept of pre-COPD and preserved ratio impaired spirometry. However, we specifically aim to reduce heterogeneity by grouping patients according to the cause of their COPD and possibly similar pathophysiology.
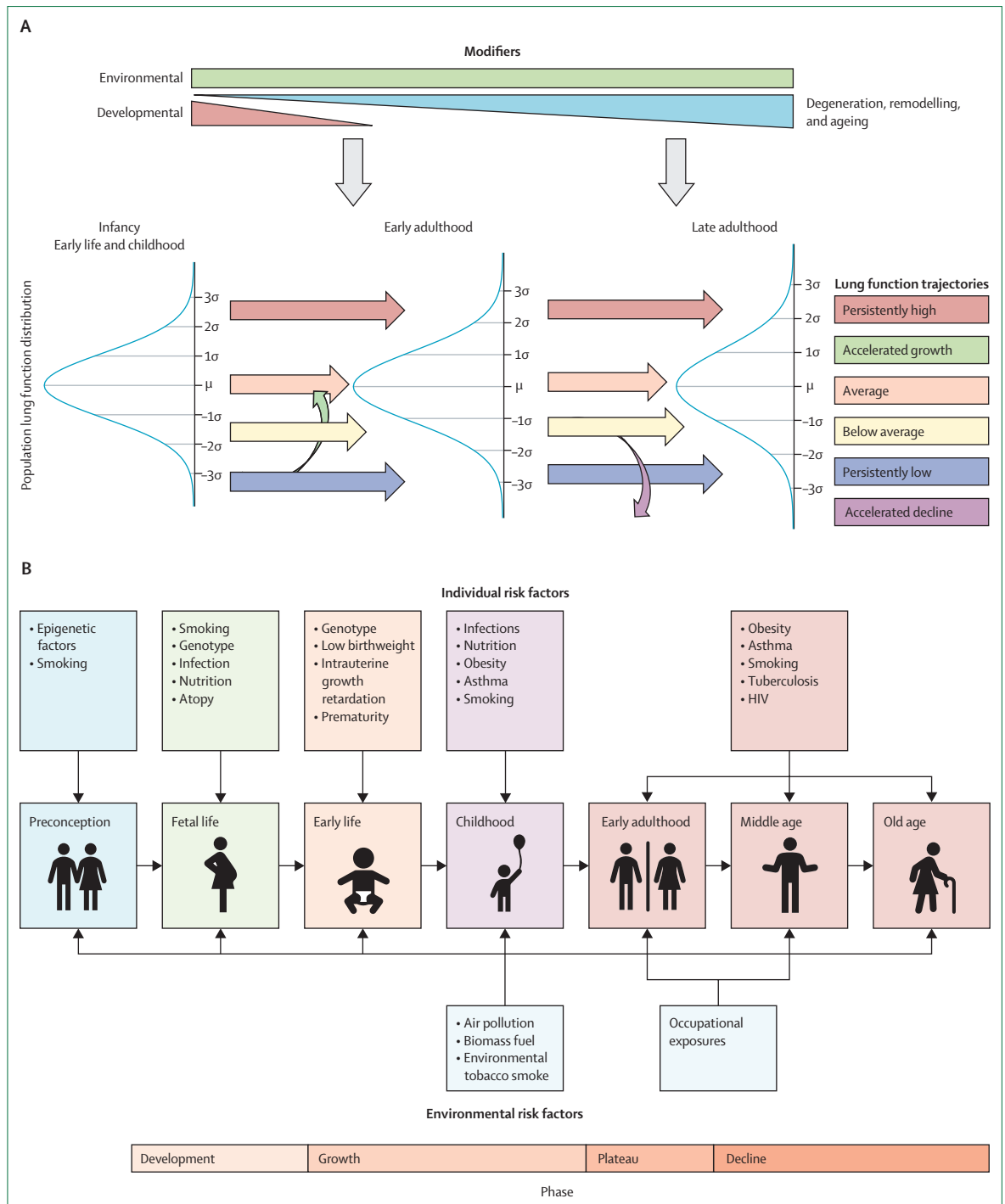
Figure 9: Lung function trajectories across the lifecourse (A) and environmental and individual risk factors that affect lung function trajectories and lung health from before conception to old age (B)

Varied histopathological changes

The heterogeneity of COPD pathology is evident in the wide variation in the extent of airway remodelling, including smooth muscle alteration and fibrosis, airspace enlargement as noted in emphysema, inflammation, and vascular changes across patients grouped on the basis of the presence of airflow limitation (figure 10). Many of these pathophysiological changes are not included in current diagnostic algorithms.

Airway remodelling is characterised by differences that include the fractional area of elastic fibres, as well as variations in the extent of epithelial changes, such as goblet-cell metaplasia and squamous metaplasia.[167] Moreover, airway smooth muscle content is increased in COPD, albeit to a lesser extent than in asthma, but is highly variable between patients. Emphysema is another hallmark of COPD that is driven by numerous complex pathological changes, including impaired tissue repair and regeneration, but its severity varies substantially between patients. In addition, inflammatory cells lead to apoptosis and degradation of the extracellular matrix due to the release of proteinases, oxidants, and cytotoxic products but the intensity of these effects also varies. Collagen degradation is upregulated, particularly during exacerbations, and the non-uniformity of this degradation within the lung affects disease presentation.[168,169]

Although an abnormal inflammatory response is central to COPD, the types of inflammation are heterogeneous: patients can have neutrophil-dominant, eosinophil-dominant, or pauci-inflammatory phenotypes based on sputum analyses. Treatment guidelines[5] suggest that a subgroup of patients with high circulating eosinophil counts respond better to inhaled corticosteroids, although there are challenges in the identification of a threshold, because a large proportion of patients with COPD have varying blood eosinophil counts.[170] A study[171] combining data from 11 clinical trials found that blood eosinophils are not a reliable biomarker for predicting future COPD exacerbations.

Although expanded knowledge of the importance of eosinophils could prove useful, most exacerbations are mediated by neutrophilic inflammation. There is increased presence of neutrophils in the airways of patients with COPD, and in biopsies taken from both the airway wall and parenchyma.[172] The degree of neutrophilic inflammation correlates with important clinical outcomes such as the rate of lung function decline and exacerbation events.[173]

The microbiome is important for lung health and perturbations in the normal microbiome, even in early life, can predispose individuals to COPD.[174] The microbiome is shaped shortly after birth and is affected by important early-life events such as antibiotic exposure and respiratory infections. Resident microbiota can also affect the risk of subsequent childhood respiratory infections, particularly viral infections, and childhood respiratory infections can in turn affect the resident microbiota. Thus, the microbiome is associated with many of the key factors influencing the development of maximal lung function in early adulthood and could potentially modulate the immune response upon exposure to cigarette smoke or environmental pollution, thereby contributing to the development of COPD. In stable COPD, patients with neutrophil-dominant inflammation mainly had a balanced bacterial microbiome, but some subgroups' microbiomes were dominated by either *Haemophilus*, *Moraxella*, or
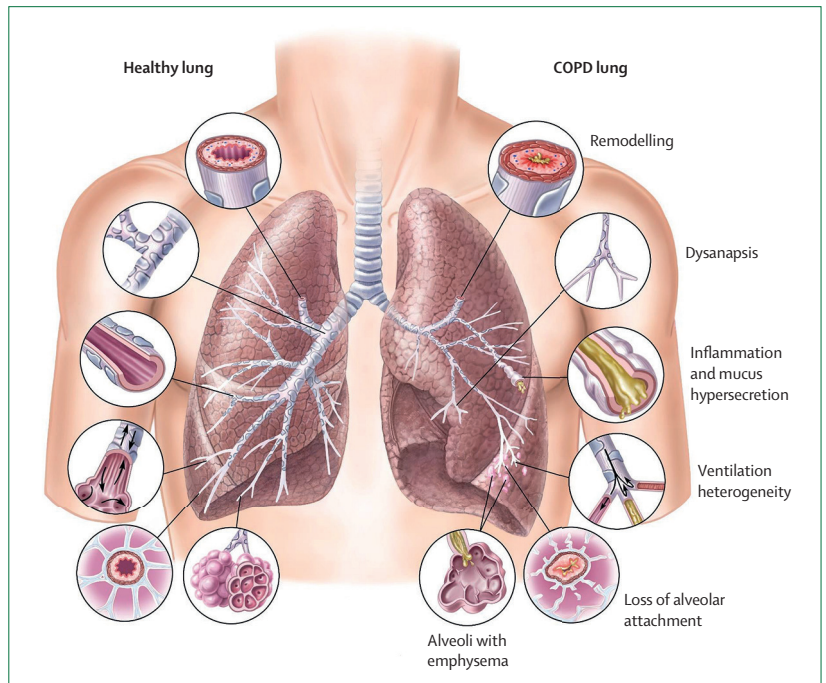

Figure 10: Comparison of physiology between healthy lungs and lungs affected by COPD
COPD=chronic obstructive pulmonary disease.

Streptococcus species.[175] Loss of microbial diversity, as measured by the richness and balance of microbial communities, is noted in patients with COPD with lower FEV_1, more frequent exacerbations, and increased mortality compared with healthy controls or smokers without COPD.[176] In patients whose inflammatory profiles are not neutrophil dominant, bacterial microbiomes are balanced during stable COPD.[177] Fungal sequences have also been detected in sputum samples from patients with COPD, and increased fungal diversity and load is associated with frequent exacerbations.[178] Treatment of COPD with inhaled corticosteroids affects the lung microbiome and the expression of epithelial genes involved in tight junction promotion, interleukin 17, and tumour necrosis factor inflammatory pathways.[179]

One suggested approach to simplify and manage the heterogeneity of COPD is to remove all diagnostic labels such as COPD, asthma, and bronchitis, and to focus instead on individual therapeutic goals and clinical, physiological, or biological characteristics that are quantifiable with biomarkers (commonly referred to as treatable traits).[180] This approach has proven useful in some settings, but its full validation and implementation are dependent on further evidence.

A proposal for diagnosis of COPD

As discussed, diagnostic guidelines do not account for the heterogeneity of the pathophysiological processes underlying COPD, which are in turn driven by the genetic determinants and cumulative lifelong environmental

exposures leading to the disease. The elimination of COPD will require both prevention of new cases and cure for those with existing disease. Thus, a novel approach to diagnosis that moves beyond spirometric criteria alone (which identifies disease only after irreversible airway damage has already occurred) is required. Current diagnostic approaches substantially underestimate the burden and morbidity of COPD and potentially prevent the development of curative treatments. Although spirometry has a long, proven history for many purposes, including epidemiological surveillance and drug

development, there is clear evidence of pronounced lung disease in those without spirometric airflow limitation that might be more amenable to treatment, including reversal of disease and cure.

Lowe and colleagues[181] used four criteria to categorise patients as having possible, probable, or definite COPD. This approach increased the COPD population by 36%.[181] The four criteria used were exposure (only to tobacco smoking), CT (≥5% emphysematous involvement, average wall thickness for a hypothetical airway with a 10 mm lumen perimeter ≥2·5 mm, or 15% air trapping), symptoms (modified medical research council scale score ≥2 or chronic bronchitis defined as chronic cough and phlegm), and spirometry (FEV_1 <80% of predicted or a FEV_1 to FVC ratio <0·70). Lowe and colleagues' diagnostic criteria are an advance on standard guidelines, but several aspects can be further improved. First, COPD is a lifelong disease, and it is crucial to account for early life and other events that impair the ability to attain maximal lung function, such as prematurity, predisposing genetics, recurrent childhood respiratory illnesses, and other infections such as HIV. Second, additional emphasis on exacerbations or acute worsening of respiratory symptoms is essential. In the group of patients with exposure only (ie, the reference group), 1% of the participants had severe exacerbations, but no data were published for mild or moderate exacerbations, which should also be considered symptoms of COPD. Therefore, the reference group already includes participants who belong in a different group (ie, the exposure plus symptoms group—possible COPD). Third, persistent airflow limitation was assessed using spirometry only, and we believe that a broader definition of airflow limitation is required.

On the basis of our current understanding of the heterogeneity of COPD, a range of exposures, symptoms, and physiological, radiographic, and pathological abnormalities could be considered in a new diagnostic approach (panel 2), although not all of the supporting testing would be required in all patients. We propose a model based on this broader range of factors that is useful and feasible in primary-care settings (including low-income settings), and also applicable in tertiary and quaternary care centres where advanced testing is available (figure 11). We advocate that the initial emphasis in the assessment process should be on identifying individuals with symptoms of cough, dyspnoea, and recurrent events concerning for exacerbations. We argue that a diagnosis of COPD should be considered even in individuals with minimal symptoms, who can still have clinically significant pathological changes. We recommend a personalised assessment strategy based on a thorough history and physical examination to identify specific high-risk features. The proposed diagnostic algorithm also suggests a category of probable COPD based solely on the presence of substantial respiratory symptoms, although this diagnosis could be complemented with

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Panel 2: Diagnostic considerations in chronic obstructive pulmonary disease

- Chronic respiratory symptoms*
  - Dyspnoea
  - Cough
  - Sputum production
- Acute worsening of respiratory symptoms*
- History
  - Premature birth
  - Childhood respiratory infections (pneumonia, viral bronchiolitis, tuberculosis)
  - Childhood respiratory illnesses (asthma, chronic lung disease of infancy)
- Exposure
  - Tobacco smoking, environmental tobacco smoke, vaping
  - Environmental exposure (indoor fuel fumes, ambient air pollution or smog, wildfire smoke, occupational exposure)
- Genetics
  - $α_1$ antitrypsin deficiency
  - Telomerase polymorphism (*TERT* gene)
  - Family history in non-smokers
- Airway remodelling*
  - Airway smooth muscle cell hypertrophy
  - Thickening of basement membrane
  - Chronic airway inflammation
  - Pathological turnover of the extracellular matrix
  - Increased airway wall thickness on CT
- Persistent airflow limitation on lung function tests*
  - Forced expiratory volume in 1 s/forced vital capacity
  - Specific effective airway resistance
  - Lung clearance index
  - Reduced peak flow
  - Nitrogen washout measures of heterogeneity
  - Forced oscillometry (difference in oscillation resistance at 5 Hz and 19 Hz, reactance area)
- Parenchymal abnormality*
  - ≥ 5% emphysematous involvement (defined as areas of lung density less than −950 HFU) on CT
  - Destruction of terminal bronchioles visible on CT
  - Decreased diffusion capacity
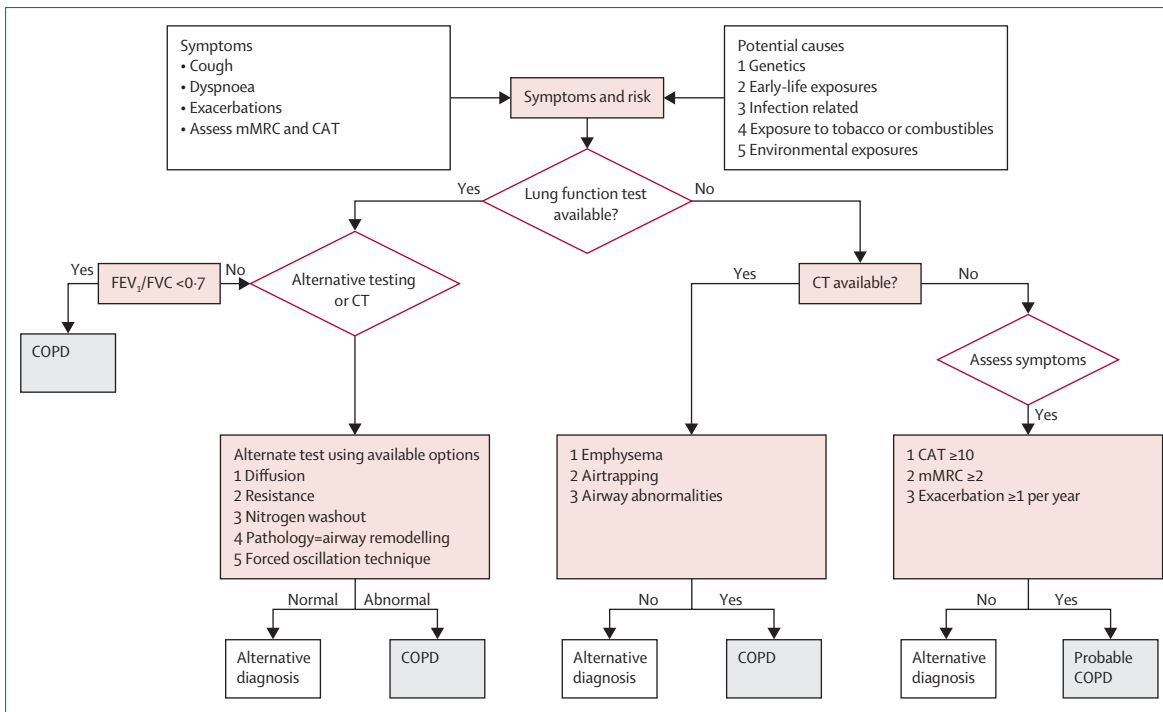
*Not explained by another condition.

Figure 11: Proposed diagnostic algorithm for COPD
COPD=chronic obstructive pulmonary disease. mMRC=modified medical research council scale. CAT=COPD assessment test. FEV$_1$=forced expiratory volume in 1 s. FVC=forced vital capacity.

inexpensive pulmonary testing, including peak flow measurements.

Although the proposed algorithm cannot be fully supported by available data, we believe that it will improve recognition of early disease, increase awareness of risk factors, and foster research around each of the COPD types. As previously discussed, these types refer to the main causative factors responsible for COPD and might be linked to specific, targetable pathophysiological processes. The emphasis on disease types allows for more targeted screening of high-risk individuals and increases recognition of underappreciated risks. The type-based approach and the diagnostic testing criteria will need to be applied sensibly and will require clinical judgment. For instance, the level of exposure to air pollution that would put someone at risk for type 5 COPD is debatable, because there is no definitive safe threshold. If data were available to estimate the risk of disease against a reference standard, the development of a weighted model could refine risk stratification, but such sophisticated models are yet to be developed. However, we still believe that clinicians can use the proposed model to approach potential disease.

Utility of symptoms and types in diagnosis

We believe that identification of symptoms is essential for prompting assessment and as a diagnostic tool even in settings where lung function testing or imaging are unavailable. Our model focuses on the identification of

individuals with cough, dyspnoea, and a history of exacerbation events. After recognition of symptoms, we advocate for assessment of symptom burden potentially related to COPD using the modified medical research council scale or the COPD assessment test. The Commission places a high value on the recognition of symptoms, which are prognostically important and could themselves define disease. We examined the usefulness of symptoms alone, and in combination with spirometry and CT data, to predict exacerbation risk in 10 000 patients enrolled in the COPDGene study (appendix p 6). We found that models including only demographics and symptoms did well in predicting exacerbation events and that the addition of spirometric or CT data only moderately improved the model (figure 12).

These models were designed to assess exacerbations and not as a diagnostic tool, but this information highlights the importance of assessing symptoms along with the appropriate exposures in identifying clinically significant COPD. Although we do not advocate that objective physiological or imaging examinations be routinely omitted, our data suggest that in low-income settings, the combination of demographics, smoking history, and respiratory symptoms can be used to prognosticate and potentially select patients for treatment. Inexpensive pulmonary testing, including peak flow measurements, could also be included in a diagnostic algorithm for low-income areas.
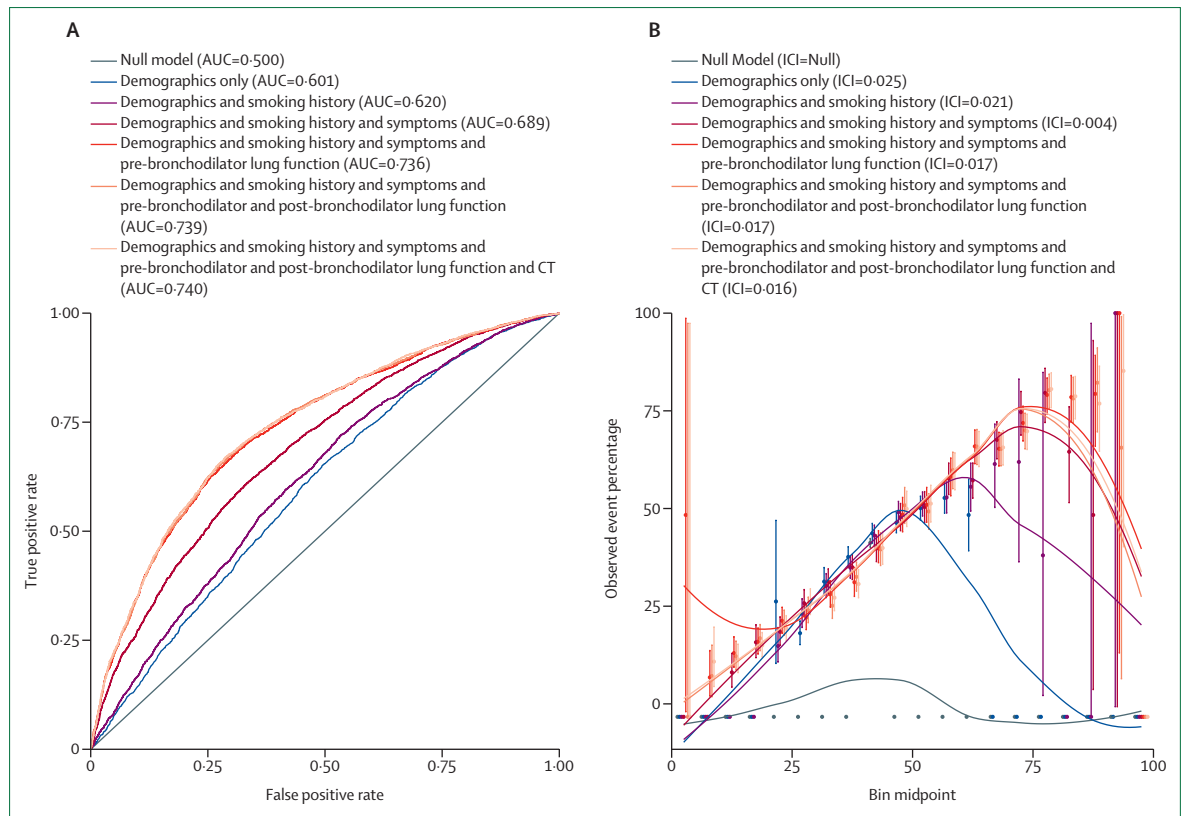
Figure 12: Receiver operating characteristic curves (A) and calibration curves (B) for prediction of exacerbations of chronic obstructive pulmonary disease
Analyses that include lung function use pre-bronchodilator measurements. Higher AUC indicates better discrimination, whereas lower ICI indicates better calibration. For more information, see the appendix (p 6). AUC=area under the receiver operating curve. ICI=integrated calibration index.

As discussed previously, there are crucial causative factors other than exposure to tobacco smoke that are highly predictive of COPD risk. The establishment of COPD types promotes increased recognition of these factors by researchers and clinicians. It is also increasingly evident that these types might be driven by different pathophysiological processes, or by varying severity of shared processes, and that each can result in clinical COPD (figure 13). Although more research is needed in this area, we believe that this framework will support the accelerated development of therapies that target the underlying pathophysiology central to specific types of COPD.

Diagnostics in symptomatic people with COPD types

Extensive efforts have been made to drive the uptake of spirometry in diagnosis of COPD. Use of spirometry is common practice, and guidelines recommend spirometric measurements of lung function before and after administration of a short-acting bronchodilator to diagnose COPD (based on the post-bronchodilator measurement). However, use of post-bronchodilator testing to establish the presence of airflow limitation adds little predictive utility beyond the information gained

from pre-bronchodilator testing, and indeed, no other chronic condition requires a similar diagnostic approach.[182] Bronchodilator response was historically thought to help to differentiate asthma from COPD; however, it is well established that not all people with asthma have fully reversible expiratory airflow limitation and that many patients with COPD have a noteworthy bronchodilator response. Therefore, bronchodilator response is neither sensitive nor specific enough to differentiate asthma from COPD, does not stratify COPD severity, and has debatable predictive value for clinical outcomes.[183] The Commission's stance is not that spirometry is good or bad, but rather that spirometry is too insensitive and that new methods (or combinations of methods) are required to adequately detect limitation of expiratory airflow and pathological correlates and to diagnose COPD (figure 11).

Alternative lung function testing

Substantial pathological changes have already occurred before limitation of expiratory airflow can be detected by spirometry. Decrements in lung function have clear prognostic value through developmental stages of life and early adulthood, even in the absence of spirometric evidence of airflow limitation. Current diagnostic algorithms fail the population of patients with COPD
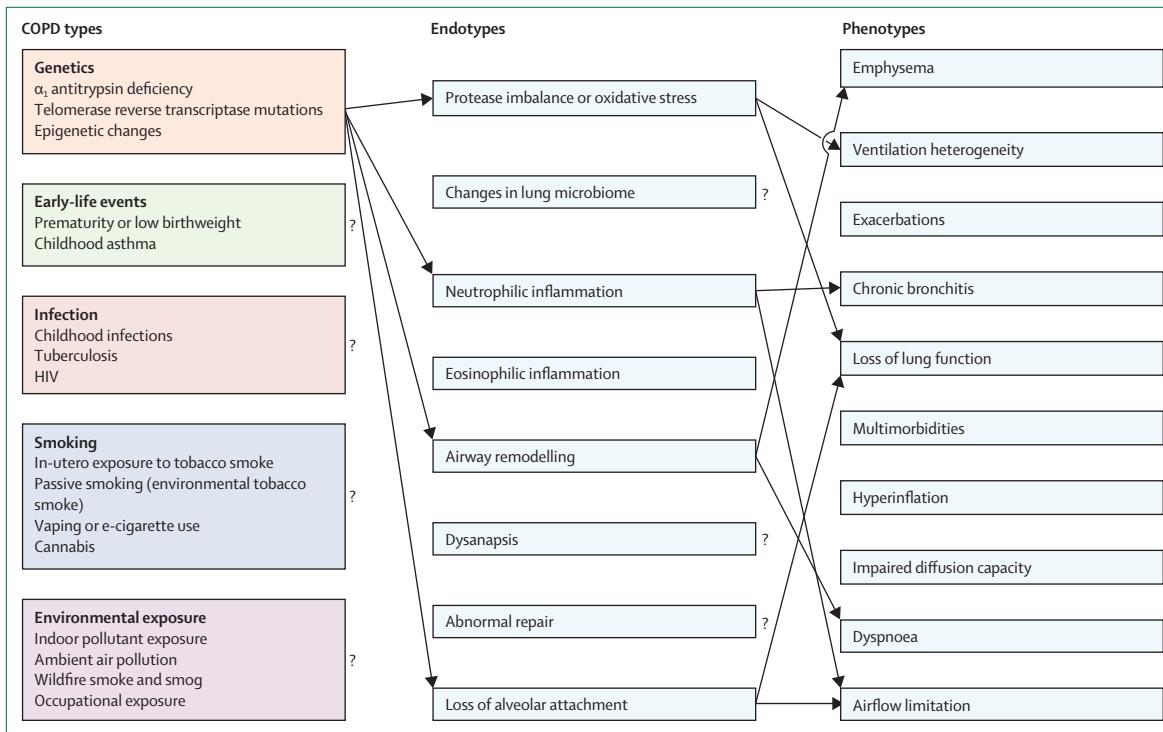
Figure 13: **Association between proposed COPD types, endotypes, and phenotypes**
The proposed COPD types probably result from varying molecular mechanisms (endotypes) that in turn result in the observable phenotypes of the disease.
COPD=chronic obstructive pulmonary disease.

who do not have detectable airflow limitation. Research in observational cohorts[2,51] has showed that low peak lung function or rapid subsequent decline in lung function, or both, is associated with increased risk of future lung disease. Low peak lung function in youth also predicts future extra-pulmonary conditions, such as heart disease, cachexia, muscle loss, depression, and renal disease.[184,185] Although the reasons for these relationships are not fully understood, their existence strongly supports the widespread implementation of routine lung function testing in young adults. Up to now, lung function has been based mainly on spirometric measurements. Some lung function tests that show promise as potential tools for identifying individuals with COPD include DLCO, resistance testing, nitrogen washout, and forced oscillation techniques (FOT). Unfortunately, none of these testing modalities have been studied as extensively as spirometry. As such, the ideal cutoffs for distinguishing normal from abnormal lung function has yet to be established for these tests.

Specific effective airway resistance (sReff) reflects the patency of airways. In a study with nearly 1000 participants,[186] sReff differentiated asthma from COPD. In another study (unpublished), sReff distinguished current smokers or ex-smokers from never smokers without spirometric airflow limitation (ie, a normal FEV_1 to FVC ratio): even though the current or former smokers did not have spirometrically defined obstruction, they still had a higher sReff than non-smokers (figure 14; appendix pp 6, 7). As expected, patients with spirometrically defined airflow limitation have a higher sReff than those without limitation. The increase in sReff evident in current or former smokers with a preserved FEV_1 to FVC ratio could be used to identify the presence of COPD at an earlier stage than spirometry.

The difference in oscillation resistance at 5 Hz and 19 Hz (R_{5-19}) and area of reactance are the main outcomes measured with FOT, but use of a range of frequencies could improve the sensitivity of the technique.[187,188] FOT is not complicated and can be used in children and elderly people. Children with respiratory symptoms have higher oscillation resistance at 5 Hz and R_{5-19} than children with no respiratory symptoms, oscillation resistance is increased in children exposed to maternal smoking, and R_5 may be more sensitive than the FEV_1 to FVC ratio for the detection in children of lung damage caused by air pollution.[189] A European Respiratory Society technical standards document[188] outlines new reference equations to establish pathology. The lung clearance index, which is measured via a multiple-breath nitrogen washout, detects ventilation inhomogeneity in central and peripheral airways. The convection-dependent conductive ventilation heterogeneity index represents ventilation inhomogeneity in pre-acinar airways, and the diffusion-
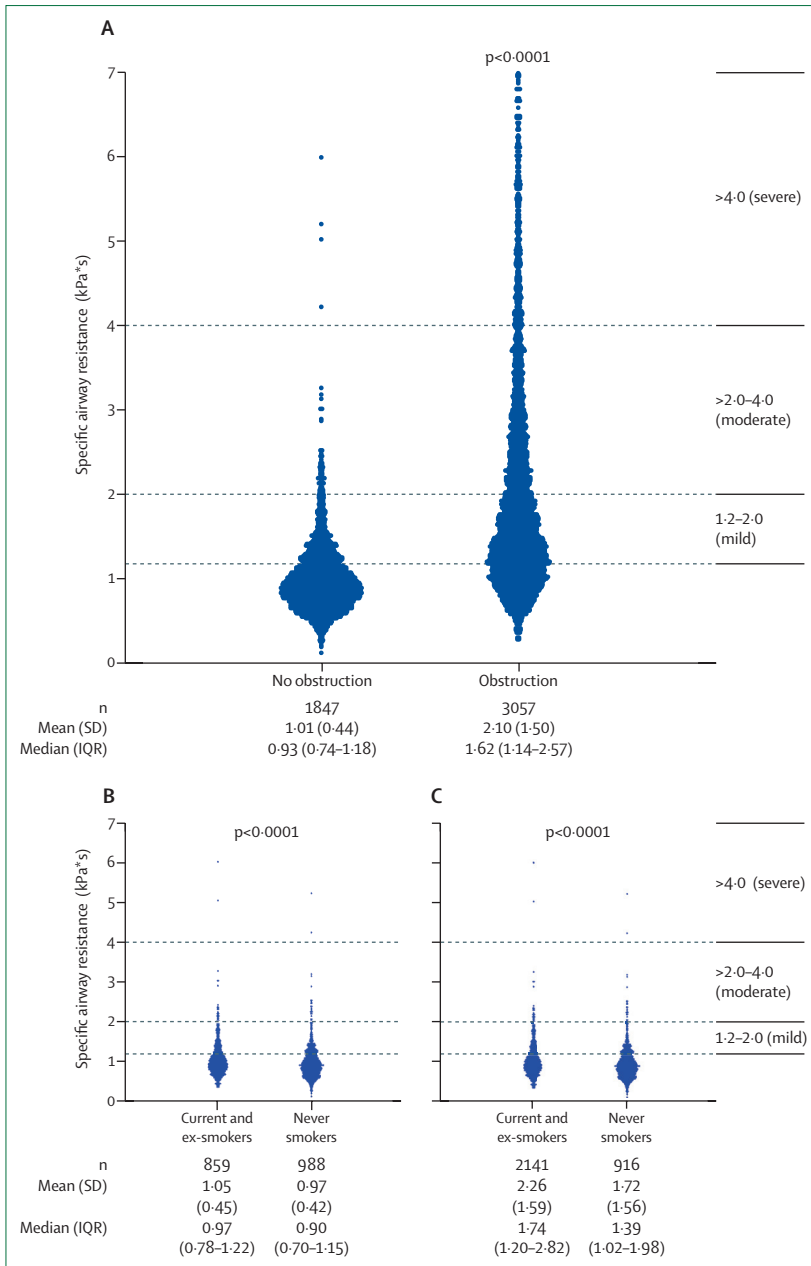
Figure 14: **Specific effective airway resistance in patients with COPD with and without airflow limitation (A); and in current and former smokers *vs* never smokers without airflow limitation (B) and with airflow limitation (C)**
Specific effective airway resistance is pathological if it is ≥1·2 kPa per s, which is further classified as mild (1·2–2·0 kPa per s), moderate (2·1–4·0 kPa per s), or severe (>4·0 kPa per s). It is higher in current or former smokers than in non-smokers, irrespective of the presence or absence of spirometrically determined airflow limitation. COPD=chronic obstructive pulmonary disease.

of residual volume to total lung capacity, and DLCO, this value was also associated with dyspnoea, exercise-induced desaturation, and exercise capacity.[191,192]

Another diagnostic tool that merits further consideration is pathological analysis of airway remodelling. Airway remodelling, including hypertrophy of airway smooth muscle cells, thickening of the basement membrane, increased airway inflammation, and pathological changes in extracellular matrix turnover, can lead to persistent airflow limitation.[167] In patients with COPD, airway smooth muscle mass increases in the small airways, and squamous epithelial metaplasia and airway wall fibrosis are present.[167,193] Basement membrane thickening was thought to be a feature only of asthma but also occurs in 40% of patients with COPD.[193] Airway smooth muscle cells contribute to airway remodelling by producing inflammatory cytokines, proteases, and growth factors. An increase in inflammatory cells such as neutrophils and T lymphocytes results in increased secretion of metalloproteinases, elastases, hyaluronidases, and chondritinases, which degrade the extracellular matrix of the lung.[194] Elastin is the main target, but collagen degradation is also upregulated and serum fragments of these core components of the extracellular matrix are associated with COPD disease severity, time to exacerbation, and overall prognosis.[168,194] COPD is also characterised by neutrophilic inflammation, but a subset of patients have eosinophilic inflammation.[195] Patients with COPD who have low blood eosinophil counts also have altered adaptive immunity, as shown by changes in concentrations of IgA, IgG, and IgM in bronchoalveolar lavage samples.[196]

As with inflammatory bowel diseases, in which endoscopies with biopsies are required for disease diagnosis and assessment of progression, a bronchoscopy, including endobronchial biopsies, should be considered a complementary approach to the diagnosis and characterisation of COPD.[197] Induced or spontaneous sputum can also be used for classification of the inflammatory profile of COPD. Eosinophilic inflammation is defined as eosinophils accounting for more than 2·5% of total cells in sputum. Neutrophilic inflammation is defined as neutrophils making up more than 61% of total sputum cells, whereas pauci granulocytic inflammation is defined as eosinophils making up no more than 2·5%, and neutrophils no more than 61%, of the total cells in the sputum sample. A mixed inflammatory profile is defined as eosinophils accounting for more than 2·5%, and neutrophils for more than 61%, of total sputum cells. However, it should be noted that inflammatory patterns can vary over time in COPD.

This expanded set of potential diagnostic tools could help to identify early COPD before spirometric airflow obstruction is detected. This list is not exhaustive, but includes methods for which some supporting evidence has been published. As uptake of our type-based classification of COPD increases, new research will refine

convection-dependent acinar ventilation heterogeneity index represents ventilation inhomogeneity close to the entrance of acinar airways.[190] Either calculated Z scores or the absolute values can be compared between patients. The slope of phase 3 of a single-breath nitrogen washout test shows the ventilation inhomogeneity of peripheral airways. In addition to associations with lung function parameters such as percentage predicted FEV_1, the ratio

the appropriate tools and cutoffs to increase diagnostic precision.

An expanded role for CT

In many settings, CT is routinely available and accessible, whereas spirometric testing can be challenging to obtain, is often interpreted incorrectly, and is insensitive for early disease (even when done correctly). An estimated 85 million thoracic CT scans are done annually in the USA alone, for reasons ranging from routine clinical care to lung cancer screening in high-risk populations.[198] Yet these images are not routinely used to assess the presence of chronic lung disease. The addition of routine radiologist or computer-assisted readings of these images could substantially increase detection of COPD, including early abnormalities, and should be immediately implemented. We also advocate that CT-detected emphysema, air trapping, and airway remodelling should be considered diagnostic of COPD, even in the absence of confirmatory spirometry. In places where spirometry is challenging to obtain but CT is available, we similarly advocate that thoracic CT be used to diagnose COPD.

Advancements in CT have led to the development of other novel metrics, including the assessment of dysanapsis and parametric response mapping, which both inform understanding of COPD.[199,200] Dysanapsis refers to the mismatch between airway tree calibre and lung growth, which was previously believed to be a physiological aberration without clinical implications. However, dysanapsis is now known to be associated with relevant outcomes and spirometrically defined COPD in older adults (mean age 63–69 years).[199] Parametric response mapping is a CT biomarker that compares functional small airway disease and emphysema with healthy parenchyma, thus helping to identify terminal bronchiole pathology. These measures, along with others in development, could prove useful in defining disease mechanisms in patients with different types of COPD, including in those with very early disease, and could ultimately lead to novel preventive and therapeutic strategies. We should embrace rather than resist this potential.

In summary, we propose a model for diagnosing COPD that captures the heterogeneous clinical and pathophysiological characteristics of the disease, reflects the importance of a range of risk factors, and expands diagnostic criteria beyond spirometry.

A crucial moment in COPD: revisiting exacerbations

Exacerbations of COPD are a major cause of morbidity, and account for more than 1 million hospitalisations annually in Europe.[201] Reducing and ultimately eliminating exacerbations is thus a crucial step on the pathway to elimination of COPD. Substantial progress in understanding of exacerbations has been made in the past few decades, but therapeutic approaches have not advanced in tandem. We aim to offer a new way forward to catalyse progress.

What is in a name?

In a European study,[202] 411 (65%) of 633 patients never or rarely used the term "exacerbation" when speaking with a nurse or physician, and physicians were unaware of its morbid implications. This problem is related to the term itself, the lack of patient and physician education about how to recognise exacerbations (and their importance), and difficulties in defining what constitutes an event. Patients with COPD and health-care providers often ignore or minimise increases in respiratory symptoms, which leads to underinvestigation of potential exacerbations and ultimately to under-reporting, underdiagnosis, and undertreatment.[203] A survey supported by the European Lung Foundation showed that 404 (64%) of 633 patients with COPD think that "crisis" is an appropriate description of how they feel during an exacerbation.[202] In the Netherlands, COPD exacerbations have been renamed COPD lung attacks; the term was introduced in a national action plan that also included an integrated care plan to reduce hospitalisations due to lung attacks and provided guidelines for diagnosis and treatment.[204]

What is in a definition?

Although many patients recognise exacerbations when they happen, an operational definition that can be used in both clinical care and research has proved challenging. An exacerbation of COPD is defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD".[5] Unfortunately, this definition captures none of the underlying processes driving the event, does not include subtyping or the use of biomarkers to categorise the event, and can lead to misdiagnosis and misinterpretation, hindering advancement in the field. Novel approaches have been proposed[6] but none have been widely adopted. By contrast, the definition of an acute myocardial infarction has undergone four revisions during the past decade and includes both objective clinical and biochemical criteria and five defined subtypes.[205] The definition of an

	Ambiguity
Sustained	What duration of symptoms defines "sustained"?
Worsening	Which components of disease are getting worse?
Beyond	Occurring after how much time?
Acute	How quickly does a symptom have to emerge to be judged "acute"?
Might warrant	Does it require or not require treatment?

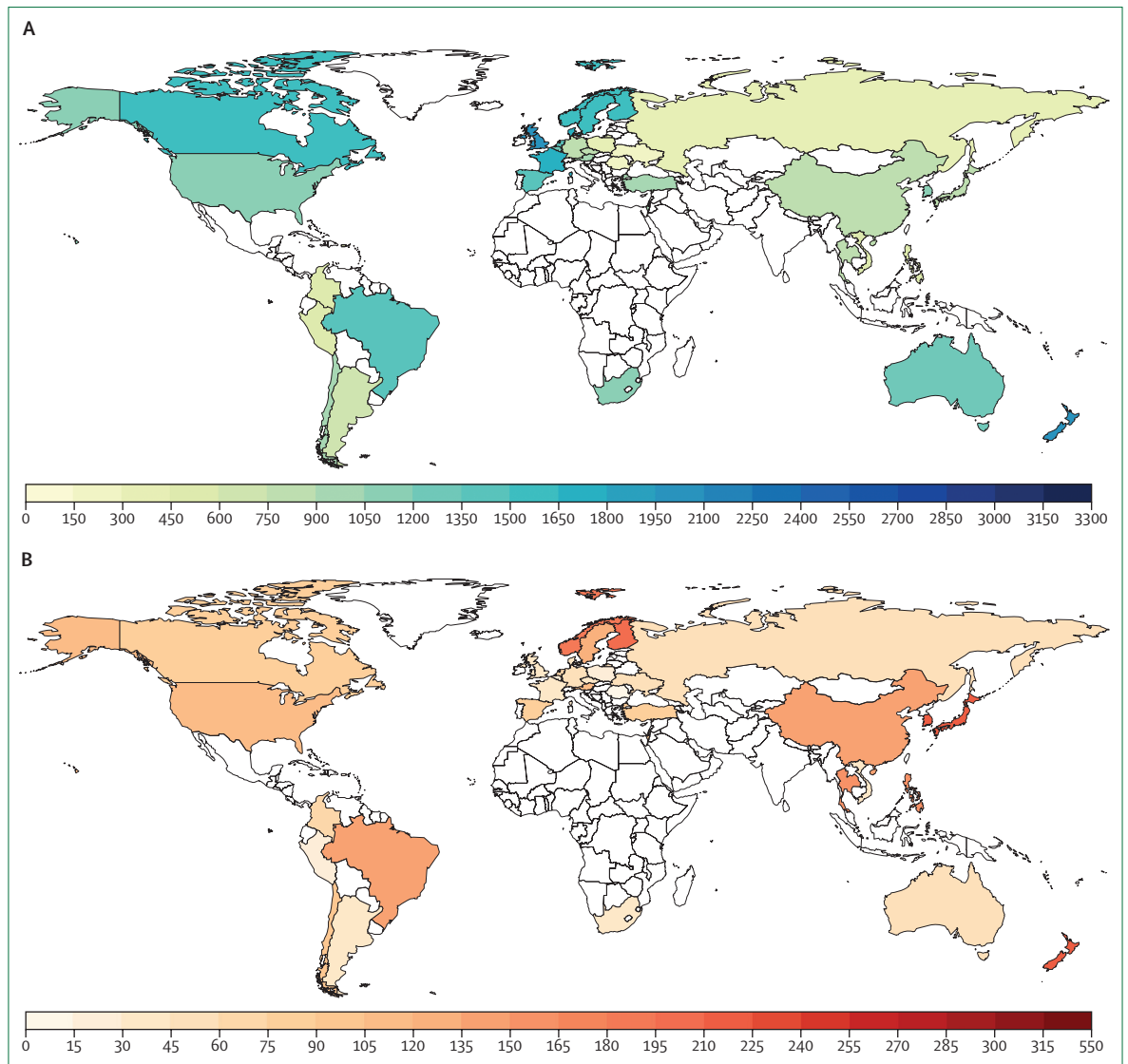*Table 4:* Ambiguous terms used to define exacerbations of chronic obstructive pulmonary disease

***Figure 15:* Maps of the incidence of moderate or severe exacerbations (A) and pneumonia (B) in patients with chronic obstructive pulmonary disease**
Data sourced from the IMPACT study.[207] This figure is redrawn with permission from GlaxoSmithKline.

exacerbation of COPD includes five terms that are at best ambiguous and at worst misleading (table 4). Furthermore, event-based and symptom-based definitions of exacerbations are not closely associated. The Anthonisen classification system has been used as an alternative definition for COPD exacerbations, but these criteria were created to capture symptoms of an acute exacerbation of chronic bronchitis that would respond to antibiotics as part of a trial design.[206]

We propose that exacerbations be defined as an augmentation of the pathophysiological process underlying COPD in individuals with increased respiratory symptoms after exclusion of alternative diagnoses. The uncertainties in identifying and characterising an exacerbation are not only patient-specific but also can be affected by cultural and regulatory differences across

countries and health systems, which can have implications for both practice and clinical trials. In the IMPACT study[207] (figure 15), for example, rates of exacerbation and pneumonia varied widely according to local definitions, standards of management and reimbursement, and national health-care organisations. In addition to the limitations of the definition of exacerbation in general, characterisation of exacerbation severity is based on the pharmacotherapy used to treat the event and the treatment setting. This approach is problematic because it is dependent on decision making by the provider and the health-care setting instead of the underlying disease process. It is therefore essential that the definition and severity assessments of exacerbations are rewritten to improve understanding of their epidemiology and to personalise management.

Why revisit diagnostic criteria for exacerbations?

Classically, a COPD exacerbation is a diagnosis achieved by excluding other possible causes for increased respiratory symptoms (eg, pulmonary embolism, heart failure, pneumothorax). However, there are no clear standardised recommendations for how to exclude these conditions in guidelines, and misdiagnosis of an exacerbation at the time of increased respiratory symptoms can lead to ineffective treatment. For example, the estimated prevalence of pulmonary embolism in patients with COPD who report worsening symptoms of dyspnoea is as high as 20%.[208] In addition, patients with COPD can experience late detection of a cardiac event, even though 25% present with increased troponin concentrations indicative of myocardial injury.[209] Failure to recognise and treat pulmonary embolism and myocardial infarction in patients with COPD has deleterious consequences. Additionally, some URTIs are associated with decreased quality of life, spirometric impairment, and increased scores on the COPD assessment test and the modified medical research council scale,[210] and yet are not classified as exacerbations in the current guidelines.

Comprehensive study of patients during an exacerbation can be difficult. Many mild events go unreported. Most moderate events are treated at home and thus blood, sputum, or other biological specimens are not obtained. Some patients with exacerbations can also be very ill, which can limit collection of detailed respiratory, physiological, biological, or radiological data. The resulting inability to appropriately classify the event hinders identification of potential triggers and the development of novel treatment targets.

The frequency of severe exacerbations (ie, requiring hospital admission) has decreased by roughly 50% since the beginning of the COVID-19 pandemic.[211] This reduction is probably attributable to social isolation and distancing, increased hand hygiene, and particularly the use of facemasks, which decisively decrease viral transmission and suggest that the main underlying cause of exacerbations is directly or indirectly virus-related. Assessment of the continued use of these measures in high-risk patients with COPD will be important after the resolution of the pandemic. For many years, exacerbations have been thought to be preceded by a URTI. A 2019 study[212] showed that URTIs led to exacerbation in 16% of cases, and for about a third of these events the same virus was detected at both the onset of the URTI and during the exacerbation. However, establishing whether a microbe is the causative agent for an exacerbation and the importance of targeting that microbe as part of treatment is complicated. The tools used for microbial detection are limited by slow turnaround times (3 days for sputum culture and 48 h for qualitative viral detection), which reduces their usefulness. Rapid PCR analysis is much faster and has consistently increased detection of microbes compared with standard culture techniques, but not all detected pathogens are clinically relevant—many patients with COPD have chronic infections with associated inflammation.[213] There is therefore no practical way to establish if the detected microbe is driving changes in airway resistance or hyperinflation or if treatment targeting that microbe will improve physiology. Furthermore, no antiviral medications have been shown to be effective in the treatment of exacerbations.

The degrees to which inflammation (pulmonary and systemic), airway resistance, changes in airway calibre, or neural respiratory drive contribute to an exacerbation are not fully elucidated. Exacerbations are clustered according to the underlying predominant inflammatory profile.[214] These exacerbation clusters are difficult to distinguish clinically but have been defined on the basis of unsupervised statistical analysis of airway mediators and include a pro-inflammatory endotype (bacteria-predominant), a T-helper-2 (Th2) endotype (eosinophil-predominant), a T-helper-1 (Th1) endotype (virus-predominant), and a low-inflammatory profile (pauci inflammatory). Identification of these endotypes of exacerbation is possible based on sputum markers (interleukin 1β) for pro-inflammatory endotypes and blood markers for Th2 and Th1 endotypes (percentage eosinophil count and CXCL10, respectively). The lack of rapid sputum and blood assays limits progress in profiling exacerbations on the basis of these biomarkers. However, the finding that some of these endotypes (eg, pro-inflammatory bacteria-associated and Th2-eosinophilic-associated exacerbations) are predictable from a stable state provides insight into underlying mechanisms and potential treatment planning.[25,215]

Identification of a single biomarker to inform treatment of an exacerbation of COPD has proven very difficult (although the fact that C-reactive protein and procalcitonin concentrations remain low in exacerbations that do not require antibiotic therapy has facilitated antibiotic stewardship).[23] It is increasingly likely that a panel of biomarkers aimed at detecting both inflammation and bacterial or viral infections will prove useful for the identification of the underlying exacerbation cause.

The systemic ramifications of exacerbations are poorly characterised. An increase in lung inflammation during an exacerbation could have important spillover effects on systemic inflammation. Surges in systemic inflammation could in turn have important negative consequences for the heart, peripheral vasculature, and gastrointestinal, renal, musculoskeletal, and bone marrow systems. Additionally, the effects of exacerbation treatments on non-pulmonary organ function are poorly characterised. Understanding the ramifications of the systemic consequences of these acute events could expedite the development of pulmonary and non-pulmonary therapeutic targets.

New diagnostic criteria for COPD exacerbations

Exacerbations should be framed as an increase in respiratory symptoms due to an augmentation of the pathophysiological process underlying COPD in the absence of an alternative diagnosis. To operationalise this, we suggest that an exacerbation should be defined as an increase in cough, dyspnoea, or sputum production and at least one of an increase in airflow limitation or ventilation heterogeneity, an increase in airway or systemic inflammation, or evidence of bacterial or viral infection, in the absence of evidence of acute cardiac ischaemia, congestive heart failure, or pulmonary embolism.

Bacterial exacerbations requiring antibiotic treatment occur across a continuum that includes infection limited to the airways and varying degrees of parenchymal invasion that often meet diagnostic criteria for pneumonia. In fact, pneumonic exacerbations occur in 20–36% of patients with COPD.[216] However, not all such episodes of parenchymal invasion are detectable by conventional chest radiography and chest CT might be required. Use of CT to detect parenchymal infection in patients with exacerbations should be considered to improve diagnostic precision and potentially guide alternative treatments, although we acknowledge that CT is unavailable in some health-care systems (and that costs can limit use even if it is available).

Clinicians responsible for management of exacerbations need to specify a temporal and causal relationship. A systems biology approach, which captures the effects on the lungs and other organs as well as the potential pathogens or other triggers implicated, should be advocated. All clinicians managing patients with COPD should establish the inflammatory profile of exacerbations and at a minimum relate this profile to eosinophilic or neutrophilic inflammatory subtypes and confirm whether it is bacterial dependent or independent.

To define and endotype a COPD exacerbation and delineate the underlying cause, a standardised investigation panel is required. We have proposed one such approach (table 5), for which we strongly support prospective testing and iterative improvement. Patient follow-up after an exacerbation should include reassessment of the clinical, physiological, and biological features of the event and should occur within a reasonable timeframe. We acknowledge that resources vary across countries and that the proposed panel will not be feasible in all health-care systems.

Assessment of exacerbation severity

The severity of an exacerbation should not be judged in terms of the type of treatment or the setting where treatment is provided, but rather on the basis of an objective categorisation of the degree of clinical, biological, and physiological deterioration. The Commission proposes to eliminate the definitions for mild or moderate exacerbations and to instead diagnose only severe exacerbations or non-severe exacerbations. Panel 3 details our proposal for the diagnostic and severity criteria for a severe exacerbation.

Telemedical management of deteriorations

During the COVID-19 pandemic, many clinics used telemedicine services to care for patients with COPD to comply with social distancing recommendations and prevent spread of infection to a high-risk population. Telemedicine allows medical personnel to reach patients with poor access to care, particularly in underserved populations, and it has the potential to reduce health-care costs. When patients experience an increase in respiratory symptoms indicative of an exacerbation, they frequently contact health-care practitioners by telephone. Evidence suggests that telemedicine-based symptom reporting promotes early detection of exacerbations,[217] yet there is no clear guidance on the management of patients who report exacerbation symptoms by phone. Although most telemedicine research focuses on high-income countries, telemedicine could have a greater effect in LMICs, where resources including health-care facilities and health-care providers can be scarce. Telemedicine has been used in LMICs to treat hypertension and diabetes, and to diagnose post-operative infections.[218–20] Soon after the national COVID-19 lockdown in India, use of telemedicine rapidly escalated: the government-provided telemedicine platform logged 3 million consults in 7 months.[221] For patients with COPD who live in LMICs,

	Essential	Dependent on context or presentation
Inflammation and infection		
Full blood count	X	
C-reactive protein or procalcitonin	X	
Airway microscopy and culture		X
Airway cytology (eosinophils)		X
Airway molecular testing for pathogens		X
Fractional exhaled nitric oxide		X
Hypoxia, hypercapnia, and metabolic status		
pH of venous blood gas		X
Arterial oxygen saturation	X	
General physiology		
Breathing rate	X	
Electrocardiography	X	
Lung function		X
Imaging		
Chest radiography, ultrasonography, or CT	X	
Systemic measurements		
D-dimer	X	
Renal function		X
Troponin		X
B-type natriuretic peptide		X

Table 5: Standard investigations when patients with chronic obstructive pulmonary disease seek medical attention for suspected disease exacerbation

telemedicine services could aid in the management of stable disease and the diagnosis and treatment of exacerbations. The mandatory diagnostic tools needed to assess an exacerbation include an assessment of vitals (respiratory rate and oxygen saturation), chest imaging, and blood tests (full blood count and measurement of C-reactive protein, procalcitonin, and D-dimer concentrations; table 5). To eliminate health disparities and move towards equitable access to care globally, efforts should be made to make these diagnostic tools readily available universally. This access could be accomplished through point-of-care testing or mobile diagnostic units that have basic imaging and laboratory capabilities. We suggest a COPD management algorithm, which incorporates the use of telemedicine to assess patients with suspected acute exacerbations of COPD (figure 16). Although the algorithm does include in-person appointments, if there are barriers to in-person care or times when outpatient visits are limited (such as in the COVID-19 pandemic), video virtual visits can replace in-person visits. Many examination findings that would prompt an emergency department visit can be assessed by visual inspection over camera.

Recurrent exacerbations and disease control

As with many chronic diseases, COPD can be classified as controlled or uncontrolled. Management of most chronic diseases is based on monitoring of intermediate outcomes—eg, blood pressure and hypercholesterolaemia in heart disease, glycaemia (as indicated by glycated haemoglobin A_{1C}) in diabetes. Identification of the equivalent meaningful intermediate endpoints in COPD is crucial because so far the disease has been classified only as stable or exacerbated. A patient with controlled COPD experiences mild or no symptoms, no effects on quality of life or exercise capacity, no exacerbations, and no decreased life expectancy. The term uncontrolled COPD refers to progressive or prolonged respiratory symptoms with or without recurrent exacerbations that are associated with reduced quality of life and decreased life expectancy. The patient group now referred to as frequent exacerbators constitute part of the uncontrolled COPD population, but so do patients with persistent symptoms and impaired health status despite maintenance treatment. Patients with uncontrolled COPD should have their therapeutic regimens intensified. Additional pharmacological and non-pharmacological treatments should be considered, and there should be less acceptance of ongoing symptoms.

In patients with chronic airway disease (including asthma and COPD), day-to-day lung function can vary.[222] In the BIOAIER cohort,[222] patients were stratified into four clusters on the basis of FEV_1 fluctuation over 1 year. Fluctuation clusters were partly independent of clinical diagnosis; however, COPD was mainly associated with the most severe cluster (ie, the most severe fluctuation

> **Panel 3: Classification criteria for severe exacerbations of chronic obstructive pulmonary disease**
>
> - Use of accessory respiratory muscles or paradoxical chest wall movements, or both
> - Clinically significant hypoxaemia and new or worsening hypercapnia or respiratory acidosis
> - Reduced alertness (eg, confusion, lethargy, coma)
> - Failure to respond to initial medical management
> - Right heart failure, cardiac ischaemia, haemodynamic instability, or clinically significant arrhythmia
>
> The presence of any one of these criteria is sufficient to define an exacerbation as severe. A total severity score (range 1–5) can be calculated based on the total number of criteria that are met.

phenotype). Strong differences in mechanical impairment of the lung (eg, airway obstruction, reversibility, diffusion capacity) independent of type 2 inflammation and substantial differences in exacerbation frequency were noted among the four clusters.[222] Consistent with these findings, a study[223] in patients with severe asthma indicated that airway remodelling as detected by CT was associated with acceleration in age-related lung function decline and with exacerbation frequency. Similar findings are likely to be found for COPD. A lung mechanical model was proposed to explain how alterations in lung mechanics and remodelling can lead to increased exacerbation frequency independent of the underlying inflammatory process.[224] The model predicts that altered structure–function interaction could contribute to a self-perpetuating persistent exacerbation pattern, which almost certainly requires novel therapeutic strategies.

Difficulties in treating COPD exacerbations

Randomised clinical trials of treatments for COPD exacerbations have largely focused on pharmacotherapy with antibiotics, bronchodilators, and corticosteroids, oxygen and non-invasive ventilation to tackle respiratory compromise, and pulmonary rehabilitation to tackle both the pulmonary and the systemic consequences.[5] Use of bronchodilators, systemic corticosteroids, and antibiotics as the gold standard for treatment of exacerbations is largely independent of the patient's presentation and the pathobiology driving the event. As a result, there are no specific disease-modifying therapies targeting exacerbations or the contributing pathways, including hypoxic tissue injury, apoptosis, and necrosis. This absence contrasts with the innovative treatments available for acute myocardial or neurological infarctions, which target tissue hypoxia, prevent cell death, and foster cell regeneration.[225,226]

Disappointingly for patients and health-care practitioners, there are no dedicated efforts by relevant stakeholders to change the acute treatment of an
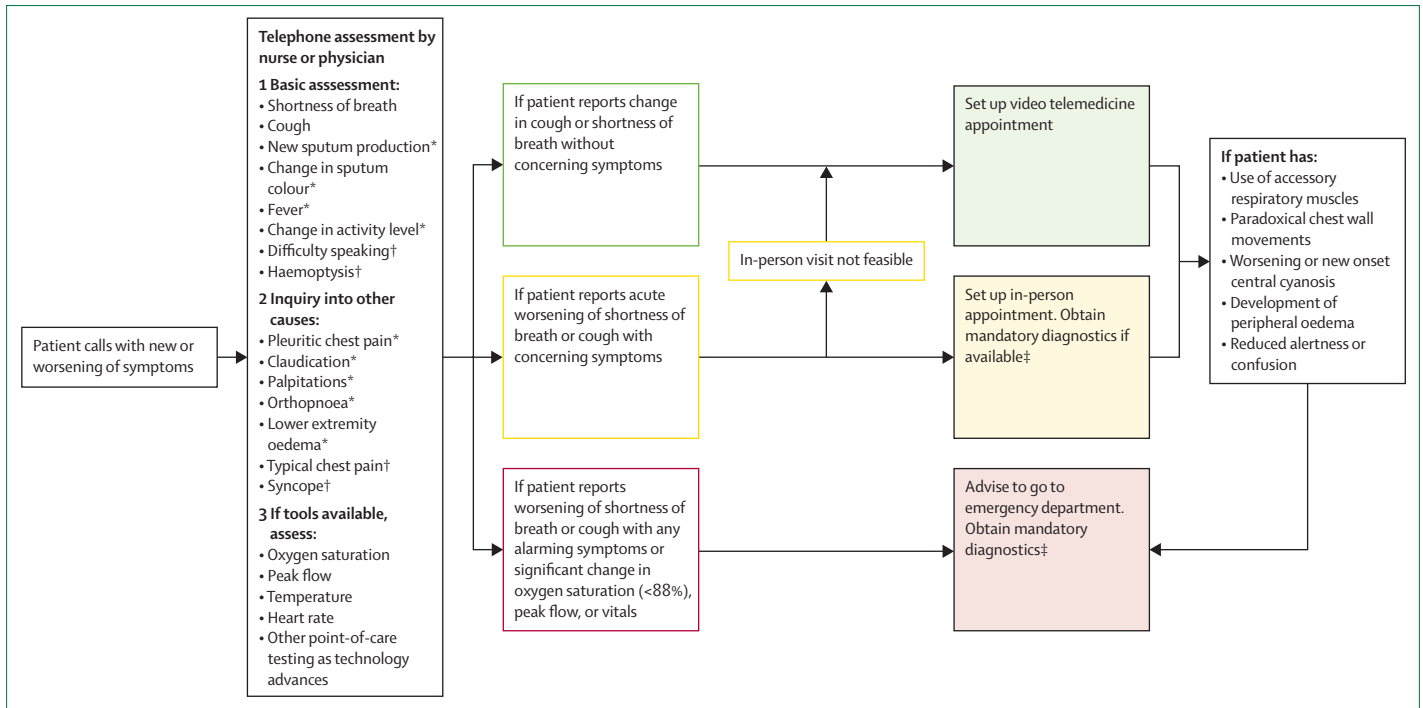
Figure 16: Flowchart to assess the status of patients with chronic obstructive pulmonary disease with new or worsening respiratory symptoms who contact medical personnel by telephone

*Concerning symptoms. †Alarming symptoms. ‡Mandatory diagnostics include respiratory rate, oxygen saturation, chest image, full blood count, and measurement of C-reactive protein and D-dimer.

exacerbation. Furthermore, despite poor treatment responses in many patients[25] and the substantial burden of harm,[227] guidelines continue to advise the use of systemic corticosteroids for most exacerbations, an approach that was first assessed more than 40 years ago.[228] Moreover, national and international guidelines and Cochrane systematic meta-analyses[229] have stated that no further evidence is needed to establish the role of corticosteroids in exacerbations. Thus, trials of novel treatments have been complicated, because they have to include corticosteroids as standard of care in the comparator group, the efficacy of which is questionable in many cases. The use of self-management strategies, including so-called rescue packs of corticosteroids and antibiotics, is widespread and is associated with overtreatment and no clear evidence of benefit.[230] Furthermore, most COPD therapies developed by the pharmaceutical industry and marketed for reducing exacerbations are based on results of short-term clinical trials of inhaled medications directed only at the pulmonary component of exacerbations with narrow patient populations that are enriched to show treatment efficacy but not treatment effectiveness. These respiratory-centric treatments have limited effects on the multisystem pathobiological manifestations of COPD exacerbations.

Outcomes after exacerbations

The inescapable truth is that outcomes after COPD exacerbations that lead to hospitalisation have remained poor worldwide. An index event could be associated with inpatient mortality of roughly 10%, and all-cause mortality of up to 50% 2 years later.[5,231] Many factors contribute to these poor outcomes, including inadequate definition and classification of exacerbation severity, poor understanding of the underlying biological processes (augmented by a lack of standardisation in capturing the pulmonary and systemic manifestations), and the scarceness of effective treatments. Outcomes after COPD exacerbations are reported in terms of readmissions, mortality, and treatment failure, which can include readmission and mortality within 30 days of the primary event. These outcomes do not attempt to differentiate physiological, biochemical, or structural changes and instead reflect poor responses to the limited treatments tried at the time of an exacerbation.

The detrimental effect of exacerbations on disease progression and quality of life are known and the reduction and eventual elimination of exacerbations should thus be prioritised. Urgent action is needed to establish a standard assessment at the time of an exacerbation, explore and implement endotype-specific treatments, and monitor physiological and patient-centred outcomes after exacerbations.

How can COPD therapy be more effective?

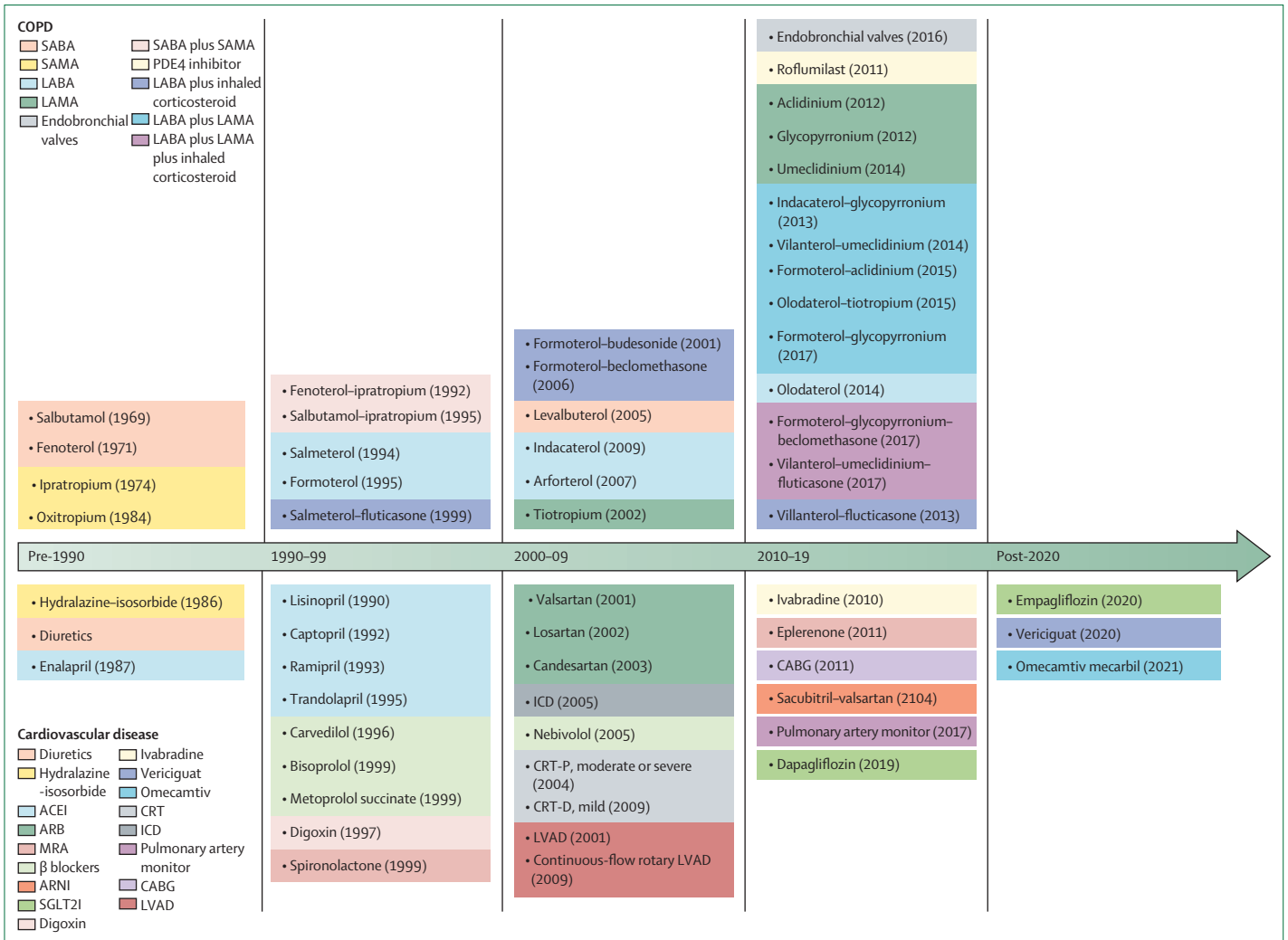Currently, COPD care starts after the presence of persistent airflow limitation is spirometrically confirmed

Figure 17: Timeline of medications entering the market for COPD *vs* cardiovascular disease
COPD=chronic obstructive pulmonary disease. SABA=short-acting β agonist. SAMA=short-acting muscarinic antagonist. LABA=long-acting β agonist. LAMA=long-acting muscarinic antagonist.
PDE4=phosphodiesterase-4. ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. MRA=mineralcorticoid receptor antagonists. ARNI=angiotensin receptor–neprilysin
inhibitor. SGLT2I=sodium-glucose linked transporter 2 inhibitor. CRT=cardiac resynchronisation therapy. ICD=implantable cardioverter defibrillator. CABG=coronary artery bypass graft. LVAD=left-
ventricular assisted device. CRT-P=cardiac resynchronisation therapy pacemaker. CRT-D=cardiac resynchronisation therapy defibrillator.

in a person with dyspnoea, exercise limitation, cough, or sputum production. Available pharmacological therapies focus on symptom relief, improvement of lung function, and reduction of the risk and frequency of exacerbations. Some data suggest that pharmacological treatments are associated with improvements in survival, but only in subsets of patients with severe disease—and even then some scepticism surrounds the results.[47,48] COPD drug development has largely focused on two main therapeutic classes (figure 17): bronchodilators (short-acting, long-acting, and ultra-long-acting, given either alone or in-combination) and inhaled corticosteroids. These treatments are given to different patient groups according to the severity of airflow limitation and previous exacerbation history. Even though COPD is the third leading cause of death worldwide, there are currently only

780 ongoing therapeutic clinical trials related to the disease, compared with more than 41 000 trials of cancer treatments. This lack of research partly explains the fact that only one new drug class has been approved for COPD in the past three decades.[232]

A global analysis[233] in 2019 also showed that only 31% of molecular targeted therapies under investigation in COPD were classified as first in class, compared with an average of more than 40% across all other indications. The scarcity of new drugs is due to not only an underpopulated pipeline, but also consistent failure to translate promising experimental and early clinical data into positive phase 2 and 3 trials.[234,235] A possible explanation for this failure is the unrealistic expectation that one blockbuster drug will lead to lung function improvement or to a reduction in exacerbations in all

patients defined primarily by the presence of airflow limitation on spirometry. It is important to remember that COPD is heterogeneous, with many endotypes and phenotypes reflecting diverse pathophysiological mechanisms, and that outcomes other than airflow limitation and exacerbation are needed, especially in early disease.

The reluctance of drug manufacturers to invest in new drugs that target a restricted patient population is perhaps understandable in view of the cost of phenotyping, the complexity of study design given the lack of surrogate markers, and the myopic view of regulatory agencies about endpoints suitable to support drug approvals. This situation must change. The outcomes that define treatment success have a major influence on which drugs will ultimately enter clinical practice. Research into COPD treatments has been dominated by a focus on lung function (especially FEV_1) to define the disease, indicate severity and prognosis, and assess the efficacy of treatments. As a result, in most studies done in the past 20 years FEV_1 is either the primary endpoint or a key secondary endpoint. In view of this FEV_1-centric approach to therapeutic development, it is not surprising that nearly all drugs licensed by regulatory authorities in the USA or EU are bronchodilators. Now is the time to embrace innovative approaches, including imaging endpoints and digital technologies such as monitors that assess physical activity, cough, dyspnoea, and other symptoms. Use of such technologies would allow daily and remote monitoring of COPD to establish how patients feel, function, and survive and thus to establish the effectiveness of a therapy in real-world settings. The five COPD types we proposed could plausibly serve as a further phenotyping tool for grouping patients with similar pathophysiology who are thus likely to respond to similar therapeutic options. Only relevant clinical trials in these COPD types could prove or refute this hypothesis, although similar approaches have proved useful in other conditions, including pulmonary hypertension, heart failure, diabetes, and cancer. In lung cancer, for example, patients are grouped according to the pathophysiology of their disease—ie, non-small cell lung cancer versus small cell lung cancer (and also based on targetable mutations)—and treatment is adapted accordingly. For example, patients with type 3 COPD (ie, infection-related COPD) might have overwhelmingly neutrophilic airway inflammation and therefore benefit more from an anti-neutrophilic medication, whereas those with type 4 COPD (associated with environmental exposure) might have more eosinophilic airway inflammation and would therefore not benefit from such treatment.

A curative approach that reverses organ damage would ultimately be needed to eliminate COPD, but before such treatment is available, patients should at the very least be able to achieve disease control in the short-term. Available therapies have enabled this goal to be partly achieved in some patients. However, pharmacological and non-pharmacological therapies have differing efficacy and many limitations.

Available COPD treatments
The most used therapeutics for COPD include anticholinergics, β_2 agonists, inhaled corticosteroids, macrolides, mucolytics, and phospdiesterase-4 inhibitors, all of which have differing mechanisms of action (table 6). Non-pharmacological treatments of COPD complement pharmacotherapy to bring about

	Mechanism of action
Anticholinergics	Block the muscarinic acetylcholine receptor to reduce bronchoconstriction
β_2 agonists	Stimulate β_2 receptors, thereby increasing cAMP and relaxing bronchial smooth muscle
Inhaled corticosteroids	Inhibit the recruitment and survival of inflammatory cells in airways
Macrolides	Inhibit bacterial RNA-dependent protein synthesis
Mucolytics	Reduce viscosity of mucous secretions; potential anti-inflammatory effects
Phosphodiesterase-4 inhibitors	Inhibit phosphodiesterase-4, thereby reducing breakdown of cAMP, which leads to bronchodilation and decreased inflammation

cAMP=cyclic adenosine monophosphate.

Table 6: **Established pharmacological treatments for chronic obstructive pulmonary disease**

	Comments
Smoking cessation	Combined counselling and pharmacotherapy are required to optimise quitting success; pharmacotherapies have differing mechanisms of action
Pulmonary rehabilitation	Improves respiratory and other muscle strength, cardiovascular function, mental health, self-efficacy, and adherence to improvements in physical activity and overall quality of life
Endobronchial valves	One-way valves placed in a target lobe that cause lung deflation, improving mechanics of breathing and expiratory airflow
Lung volume reduction surgery	Resection of emphysematous lung reduces overall lung and thoracic volume, improving mechanics of breathing and expiratory airflow
Non-invasive ventilation	Reduces the work of breathing, allowing a larger tidal volume for a given respiratory effort, which improves alveolar ventilation
Oxygen supplementation	Ameliorates tissue hypoxia by increasing blood oxygen saturation, thereby improving exercise tolerance
Targeted lung denervation	Selective denervation of cholinergic nerves surrounding the main bronchi by targeted administration of radiofrequency waves via bronchoscopy resulting in bronchodilation and reduced mucus secretion
Lung transplantation	<5000 procedures annually worldwide; new transplantation guidelines do not favour patients with COPD

COPD=chronic obstructive pulmonary disease.

Table 7: **Established non-pharmacological treatments for COPD**

improvements in symptoms and quality of life, prevent disease progression, and improve survival.[5] They include behavioural changes, such as smoking cessation and self-management, pulmonary rehabilitation, comprehensive, integrated care by a multidisciplinary team, surgical intervention, medical devices such as endobronchial valves, home oxygen therapy, non-invasive ventilation, and palliative care (table 7). Unfortunately, many pharmacological and non-pharmacological therapies are not available in LMICs. If they were deployed in LMICs, there could be major benefits at the patient and public health levels.

What is required to achieve COPD control?

For maximum effect and to ultimately eliminate the disease, new COPD therapies must be precise and target the specific molecular pathways or endotypes responsible for disease expression. These therapies might be more effective versions of the inhaled or orally administered small molecules that are already available, but could also include stem-cell or other regenerative approaches, nanotechnology delivery systems, or gene therapy. The prospects for the development of these treatments (and the associated timeline) are uncertain, although all are under active investigation. Unfortunately, although available treatments improve some important disease manifestations, several needs remain unmet, including the elimination of respiratory symptoms and tissue inflammation, reversal of airway remodelling, lung regeneration, and control of secondary systemic pathology.

Elimination of respiratory symptoms

Cough and sputum production

Mucociliary dysfunction is an important part of the pathogenesis of COPD and dysregulation of airway mucins is a key pathological process.[236] Mucociliary dysfunction also results in chronic bronchitis, one of the historical defining features of COPD. Targeting mucociliary clearance has proved challenging, despite evidence that sputum production is linked to both poor quality of life and survival in COPD.[236] The only mucoactive drugs in use are cysteine derivatives (eg, carbocisteine, erdosteine) and roflumilast, although the benefits of these drugs are debated and none are available globally. Novel treatments under investigation include bronchoscopic delivery of liquid nitrogen to destroy and denude the epithelial layer (including hyperplastic goblet cells).[237] The epithelium regenerates rapidly after the procedure and matures into a more normal epithelium within 3 or 4 weeks. An alternative approach is rheoplasty, in which non-thermal pulsed electrical fields are used to ablate the epithelium, which again regenerates as normal epithelium. CFTR modulators have revolutionised care and outcomes in patients with cystic fibrosis, and studies[238–42] suggest that some patients with COPD might also have acquired CFTR dysfunction, which could be amenable to similar treatments. However, it is unclear

whether these drugs will progress to phase 3 trials, because their effect on lung function is modest and thus the risks of investing in further development are substantial in the current regulatory environment.[242]

Dyspnoea

The level of dyspnoea experienced by patients with COPD is a better indicator of health-related quality of life than is FEV_1 and does not necessarily correlate to any objective measure of lung function, hypoxaemia, or exercise capacity. Morphine is used as a palliative treatment for chronic dyspnoea in COPD but social stigma and concerns about real and perceived side-effects, including respiratory depression and dependence, limit access to it in clinical practice.[243] Novel and safer approaches are needed. Some evidence suggests that acupuncture point stimulation could improve exertional dyspnoea in COPD, perhaps through the release of endogenous opiates.[244]

Exacerbations

Viral and bacterial infections are common in individuals admitted to hospital with COPD exacerbations. Some studies[212,245] have suggested worse outcomes in exacerbations triggered by viruses than in those triggered by bacteria. Rhinoviruses, influenza viruses, and respiratory syncytial viruses are the most common viruses detected, but few antiviral agents are available.[246] Some evidence suggests that targeting intercellular adhesion molecule-1 (which facilitates rhinoviral infection of the respiratory epithelium), the immunoproteasome (which governs viral related inflammation), or the interleukin 33–interleukin 13 axis (which drives many viral infections) could be beneficial, but more work is needed.[247–49] During most exacerbations that occur after viral URTIs, the original virus that caused the URTI can no longer be detected.[212] It is tempting to hypothesise that the virus catalyses inflammatory processes associated with the exacerbation and thus that anti-inflammatory treatments should be explored in addition to antivirals. One strategy is to counteract changes in the extracellular matrix by giving glycosaminoglycans such as hyaluronic acid or heparan sulfate. A placebo-controlled randomised trial[250] showed that high-molecular-weight hyaluronan ameliorated respiratory failure in patients with severe COPD exacerbations. Several antivirals are also in the pipeline, including a dry-powder formulation of ribavirin.[251] Modest evidence suggests that influenza vaccination could reduce COPD exacerbations.[252] COVID-19 vaccines are likely to reduce infections in patients with COPD, but no vaccines are available for rhinovirus or respiratory syncytial virus, which would probably have more substantial benefits.

Stratification of treatment based on Th2 biology and the degree of eosinophilic inflammation at the onset of an acute exacerbation was first investigated in a single-centre placebo-controlled pilot study published in 2012.[25] In one

group, systemic treatment with prednisolone was given at the onset of an exacerbation (standard treatment) whereas in the other only patients in whom more than 2% of peripheral blood cells were eosinophils were given prednisolone (the other patients in the group were given placebo). The primary outcome of the study, non-inferiority, was met, which suggests that prednisolone prescriptions could be safely reduced by 50%.[25] Furthermore, in secondary analysis, patients who received prednisolone without the biological endotype (low blood eosinophils) experienced worsened symptoms and treatment was more likely to be unsuccessful compared with patients with the same endotype who were given placebo.[25] The results of a multicentre trial[253] of eosinophil-directed systemic corticosteroid treatment in patients hospitalised with severe COPD exacerbations also showed that stratification of treatment based on blood eosinophils reduced corticosteroid exposures without increasing treatment failures. Studies of the use of anti-eosinophil monoclonal antibodies at the time of exacerbation are underway.

Elimination of inflammation

Neutrophilic inflammation

Neutrophilic inflammation is a dominant endotype in COPD and both animal and human data suggest that an imbalance between neutrophil-derived proteases and anti-proteases is central to disease pathogenesis.[254] Nonetheless, targeting neutrophilic inflammation therapeutically has been challenging not only in COPD but also in other conditions driven even more clearly by neutrophils, including cystic fibrosis and non-cystic fibrosis bronchiectasis, and no drug has yet been licensed. Drugs targeting neutrophil function—including CXCR2 receptor antagonists, inhaled PI3k delta inhibitors, and oral neutrophil elastase inhibitors—have all been tested in COPD and in general results have been disappointing, partly because of their minimal effects on lung function and an increased risk of infection.[255] Encouraging results have been reported in a phase 2 study[256] of a novel dipeptidyl peptidase-1 inhibitor, which inhibits neutrophil serine protease activity including neutrophil elastase. It prolonged time to first exacerbation in patients with bronchiectasis but has not yet been tested for COPD.

Eosinophilic inflammation

Eosinophilic lung inflammation in patients with COPD is heterogeneous. Eosinophils can be detected in biopsy specimens, bronchoalveolar lavage samples, and sputum, and often comprise more than 3% of total cells, the cutoff that is widely used to define eosinophilic inflammation.[257] Blood eosinophil counts correlate moderately with sputum eosinophil counts,[258] which has led to extensive investigation of eosinophilic inflammation as a prognostic biomarker and therapeutic target. Response to inhaled corticosteroids can be predicted on the basis of blood eosinophil counts: greater reductions in exacerbations are noted in patients with higher eosinophil counts.[259] The

licensing of anti-interleukin-5, anti-interleukin-5-receptor, and interleukin-4–interleukin-13-targeting monoclonal antibodies for asthma has led to interest in the potential effectiveness of these treatments in the eosinophilic endotype of COPD.[260,261] Trials[262] done to date have not shown consistent reductions in exacerbations, although post-hoc analyses suggest that a subgroup defined by more frequent previous exacerbation and higher eosinophil counts might be more likely to benefit.

Thymic stromal lymphopoietin (TSLP) and interleukin 33 are among a family of signalling molecules sometimes referred to as alarmins, which are released by epithelial cells after inflammatory stimulation. Release of TSLP is stimulated by a broad range of triggers, including allergens, bacteria, and cigarette smoke, and data for severe asthma suggest that tezepelumab, a monoclonal antibody that targets TSLP, improves lung function and symptoms and reduces exacerbations compared with placebo.[263] Interleukin 33 is an upstream signalling molecule that activates both innate and adaptive immune cells, and a genome-wide association study[264] showed that it is associated with risk of asthma. A trial[265] in patients with asthma showed a clear benefit with the anti-interleukin 33 monoclonal antibody itepekimab compared with placebo, and there could be subpopulations of patients with COPD, particularly former smokers, who might also benefit. In addition to potential reductions in the frequency of exacerbations, anti-interleukin-22 monoclonal antibodies could have disease-modifying effects leading to changes in the histopathological features of Th2-high inflammation, such as hypertrophy of the airway smooth muscle and thickening of the basal membrane. However, these studies[264,265] also show the challenges in translating the beneficial effects of highly specific therapies that are beneficial in asthma to the more complex and heterogeneous inflammatory milieu that is characteristic of COPD.

Lung microbiome

Modulation of the microbiome is also a potential novel therapeutic approach in COPD that could reduce chronic inflammation. Modulation could perhaps be achieved through direct approaches similar to fecal transplantation to restore the microbiota in the gut (which is used as a treatment for *Clostridium difficile* infection), but more intriguing is the potential to indirectly modulate the lung microbiome by the avoidance of unnecessary antibiotics early in life, which could reduce the selective pressure for pathogenic organisms.[266] It is also possible that the benefits of azithromycin in patients with COPD could be due to the drug's effects on the microbiome in addition to increases in the concentrations of several bacterial metabolites with anti-inflammatory effects.[267]

Reversal of airway remodelling

In addition to biologic treatments targeting Th2-associated inflammation, other agents could have the potential to

improve airway remodelling, including G protein-coupled receptor modulators, mitogen-activated protein kinase inhibitors, receptor tyrosine kinase inhibitors, non-receptor tyrosine kinase inhibitors, other kinase inhibitors, and phosphodiesterase inhibitors.[268] The reduction of hyaluronic acid in the lung caused by tobacco smoke results in increased elastolysis, which can also lead to remodelling of the airway and parenchyma.[269] Hyaluronic acid aerosol has shown promising results in mice and in early clinical trials in humans.[250]

Lung regeneration

The tissue destruction in COPD cannot be cured or reversed at present, and thus there is a large unmet medical need for novel treatment options. Emerging pulmonary regenerative medicine efforts focus on several ways to achieve lung regeneration, including activation of the endogenous repair capacity of the lungs and the development of exogenous regeneration through tissue engineering, bioartificial scaffolds, or the application of healthy progenitor or stem cells to the lungs.[270–72]

Endogenous lung tissue regeneration

Maintenance and repair upon injury of the highly complex lung structure relies on progenitor cell populations in the lung epithelium, which are tightly spatiotemporally regulated by signalling pathways.[272] Basal cells, club cells, and alveolar type II cells repopulate distal airways and alveolar epithelium after severe injury in several mouse models.[272–75] The endogenous regenerative mechanisms of the lung are severely compromised in COPD, and failure to activate core developmental pathways after injury causally contributes to the disease.[276] Therefore, activation of these pathways, which are essential for lung development and generation, could boost suboptimal repair processes, alveolarisation, and lung function.

Although many of these studies were done in animal models, the Wnt–β catenin signalling pathway initiated lung epithelial cell progenitor growth in human lung organoids and activation of alveolar repair mechanisms in lung tissue cultures derived from patients with COPD.[273] The potential to use pharmacological compounds to foster proper functioning of healthy cells and activate endogenous repair also provides an opportunity to treat COPD at much earlier stages and to potentially avoid long-term treatment that could be harmful. Early intervention could prevent structural changes and enhance the possibility of achieving lung regeneration, thus halting or even reversing the disease.

Stem-cell therapy

Mesenchymal stem cells are immunomodulatory and therefore could affect several aspects of COPD, including airway remodelling and tissue regeneration. Clinical trials[277,278] have shown that mesenchymal stem cells originating from bone marrow, umbilical cords, or adipose tissue are safe but no trials have shown efficacy in COPD. This absence of efficacy could be due to effects of the COPD microenvironment on the stem cells and further highlights that additional aspects of the pathophysiological changes in COPD need to be targeted simultaneously.[279]

Three-dimensional printing

Breakthroughs in bioengineering and three-dimensional organ bioprinting open novel avenues for potential COPD therapies. In a proof-of-concept study,[280] extracellular-matrix-reinforced biolinks were used to print human airways that had primary human epithelial progenitor and smooth muscle cells capable of differentiating into mature cells. The airways remained stable and the cells were viable for 1 month in vitro. Use of biolink-containing extracellular matrices derived from decellularised tissue is a promising new approach for generating functional human tissue and can potentially be combined with other regenerative therapy approaches to target different COPD phenotypes.

Control of secondary systemic pathology
Exercise

When properly prescribed in terms of frequency, intensity, type, and time, exercise training through pulmonary rehabilitation is a powerful physiological stimulus to restore many of the non-respiratory consequences of COPD, including deconditioning, skeletal muscle dysfunction, cardiovascular risk, and mental problems.[281] These benefits are more pronounced when exercise is combined with long-acting bronchodilators, but rates of referral to, and uptake of, pulmonary rehabilitation are low.[282] Alternative scalable methods to deliver rehabilitation in non-traditional settings, including at home via remote technologies, could substantially improve access even in rural or underserved areas.[283]

Androgenic anabolic steroids and testosterone

Hypogonadism is prevalent in 22–69% of patients with COPD and could be the result of ageing, smoking, obesity, systemic inflammation, hypoxaemia, hypercapnia, or glucocorticoid use.[284] Additionally, a link has been noted between low serum testosterone concentrations and both reduced lung function and accelerated lung function decline in both men and women.[285] Experimental evidence of the relationship between sex steroid receptors and signalling in the airways and immune system suggests that a link between sex steroid hormones and lung health is biologically plausible. In a rat model of COPD, testosterone replacement therapy attenuated pulmonary epithelial inflammation.[286] Various clinical trials of androgenic anabolic steroids in patients with COPD showed improvements in fat-free mass (ie, muscle mass), lean body mass, arm muscle circumference, weight, walking test results, and sexual quality of life compared with placebo, but none showed improvements in lung function as assessed by spirometry.[287] As is the case for

other therapeutic approaches that do not improve lung function, enthusiasm for further investigation of modification of sex hormones or other endocrine pathways has been limited.

Nutrition supplementation

Poor nutritional status has been associated with reduced lung growth and accelerated lung function decline and is a clear risk factor for the development of COPD.[288–91] Poor nutritional status could be a particularly important contributor to COPD burden in LMICs, where nutritional deficiencies are more common, and there is evidence that correction of nutrient deficiencies could improve respiratory outcomes. For example, vitamin A is important in the regulation of early lung development and alveolar formation, and in a Nepali population with chronic vitamin A deficiency, the offspring of mothers who received supplementation with vitamin A before, during, and after pregnancy had improved lung function compared with the offspring of mothers who received placebo.[288] Other data have shown associations between intake of vitamin C[289] and vitamin E[290] and improved lung function. In a systematic review and meta-analysis,[292] vitamin D supplementation reduced exacerbation frequency in patients with a baseline serum calcifediol concentration of less than 10 ng/mL, and the GOLD guidelines[5] recommend that patients hospitalised for COPD exacerbations should be assessed for vitamin D deficiency. Other data also suggest that dietary modifications might reduce COPD morbidity. Increased intake of omega-3 fatty acids, which promote resolution of inflammation, are associated with fewer exacerbations and better quality of life than increased intake of omega-6 fatty acids, which are pro-inflammatory.[293] Increased intake of the antioxidant coenzyme Q and conjugated linoleic acid both improved exercise capacity compared with placebo in patients with COPD.[294,295]

BMI is perhaps the best studied marker of the nutritional status of an individual. An estimated 25–40% of patients with COPD are underweight and 35% have severely low muscle mass.[296] Increased protein intake reduces loss of muscle mass but data for the effects of oral nutrition supplementation are inconclusive, because studies have usually combined supplementation with pulmonary rehabilitation and the amount of supplementation prescribed varied greatly. In hospitalised, malnourished patients with COPD, treatment with nutritional supplementation decreased mortality risk and increased bodyweight compared with placebo within 90 days of hospital discharge.[297] Further investigation into the effectiveness of dietary modification in reducing COPD risk and improving outcomes is clearly indicated, particularly given the low cost, safety, and broad applicability of these interventions.

At a minimum, COPD therapy should lead to disease control and the available therapies have enabled some progress towards that goal. However, many patients receiving standard-of-care treatment continue to experience symptoms, exacerbations, lung function loss, and early mortality. Novel agents will be required to achieve disease control for all patients. Ideally, treatments would intercept COPD at an early stage and allow reversal of the accumulated lung damage leading to cure. These new therapeutics will not be useful in all patients with COPD as defined by the presence of spirometric airflow limitation, and their development will rely on testing in COPD subpopulations. We believe that clustering of patients by COPD type could promote the discovery of these more potent treatments of the future.

Towards the elimination of COPD

Advocacy efforts in COPD have largely focused on raising public awareness of the disease. Such efforts include World COPD Day, which has occurred since 2002 and is typically the third Thursday in November. World COPD Day has been highly successful in mobilising COPD organisations and helping patients to find their voice. However, to prevent and eliminate COPD, fundamental changes in approaches to advocacy are required.

The Commission's proposal to classify COPD on the basis of the primary risk factor provides an opportunity for the disease to be recognised broadly—not only as a disease of smokers. People with COPD have long lived with the stigma of having a self-inflicted disease due to smoking. However, if the varied underlying causes of COPD can be better communicated, understood, and recognised, then compassion, support, and research funding could be increased.

All stakeholders in the public health domain need to recognise that the potential effects of primary prevention are immense and incomparable to any treatment that could be offered to patients with established COPD. Therefore, true elimination of COPD relies predominantly on the immediate and complete elimination of risk factors for lung disease, particularly exposure to anything other than clean air (including early-life exposures affecting lung growth and remodelling). Importantly, elimination of risk factors will not only prevent COPD; it will also help to maintain respiratory health throughout life and to promote healthy ageing. To achieve this ambitious goal, strict international and national legislation is required to eliminate exposure to irritants and toxins (eg, cigarette smoking, vaping, cannabis, air pollution, occupational exposures) throughout the life span (and prenatally), to promote improvement in maternal and perinatal care, and to minimise severe childhood respiratory infections. Furthermore, efforts to arrest disease progression and improve the lives of individuals with established disease should focus on refinement of diagnostic tools and early disease identification, increases in the efficacy and effectiveness of treatments, and equality in access to therapy. A boost in investment in research and innovation from the pharmaceutical and non-pharmaceutical sectors will be necessary to expedite progress. Finally, prevention

and care of COPD requires streamlined health systems and urgent public policy actions at a global level. Here we summarise the actions needed to progress towards the elimination of COPD.

Appreciation of overlapping and interacting risk factors

A major barrier to the advancement of COPD care is the underappreciation of important risk factors beyond smoking. Targeted efforts to reduce these risk factors and to increase knowledge and understanding of the effects of these exposures on lung growth, disease initiation, and lung function decline will pave the way to innovative treatment strategies and perhaps the possibility to eliminate COPD. Many of these risk factors for COPD are closely linked to poverty, and although beyond the remit of the Commission, elimination of global poverty would clearly contribute to the elimination of COPD.

Early-life events

To safeguard the respiratory health of future generations, policies need to be implemented to tackle early-life risk factors and improve maternal, fetal, and childhood respiratory health. Action plans should be adopted, such as those put forward by WHO to reduce preterm birth.[298] These actions could include provision of family planning services and improvements to antenatal care, patient and provider education, and the prevention and management of preterm labour. The importance of controlling childhood asthma needs to be well communicated to parents and health-care providers.

Respiratory Infections

Key actions to reduce the effects of childhood respiratory infections globally include vaccinations, adequate nutrition, and breastfeeding. Vaccination of the general population, and particularly of vulnerable groups, is extremely important and requires the involvement of all stakeholders. Major side-effects of vaccinations are very rare, and this message should be effectively communicated to the respiratory patient community and the public at large. Initiatives to encourage health-care professionals to vaccinate should be supported by professional medical organisations.

Inhalation of tobacco, drugs, and other combustible substances

The effects of exposure to tobacco smoke are clear, and targeted efforts to address environmental tobacco smoke have the potential to bring about considerable change. Exposure to environmental tobacco smoke is pronounced in the home and in private vehicles, but varies according to race and socioeconomic status, and urban versus rural residence.[299] Legislation aimed at smoke-free policies for private transportation have been implemented, but smoke-free home policies that reduce exposure to environmental tobacco smoke are not legislation-driven but dependent on
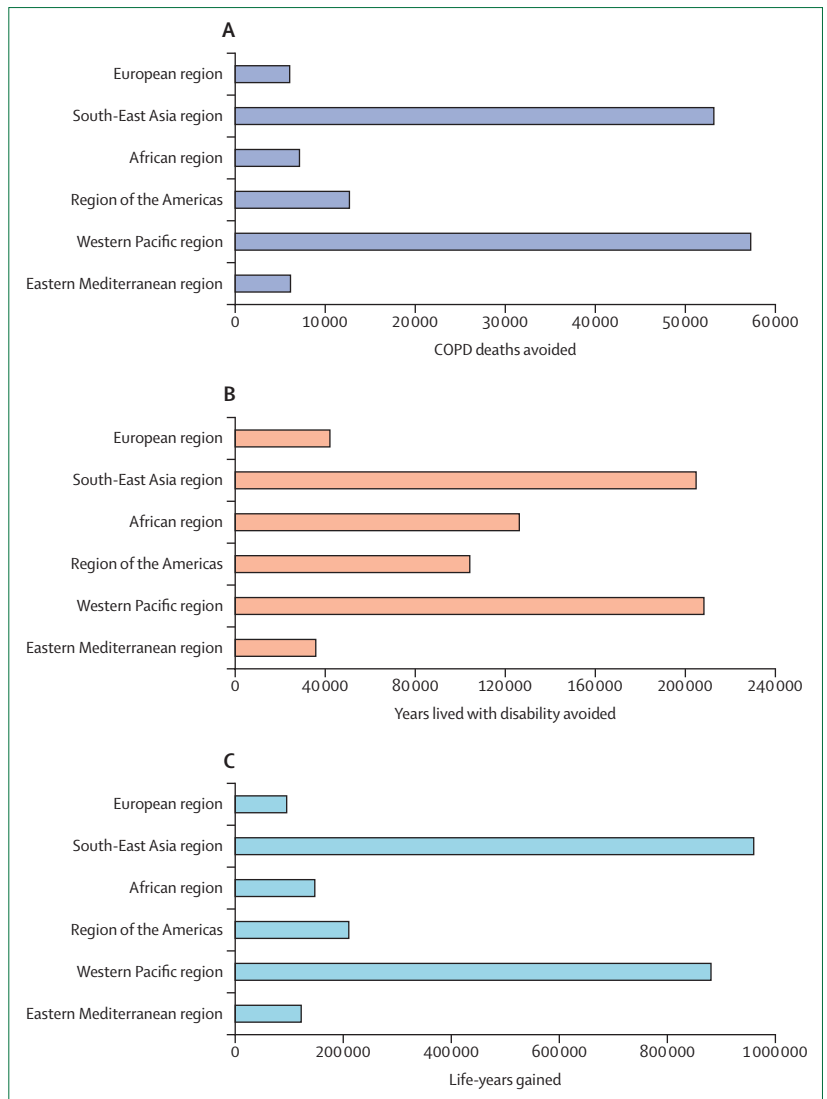
Figure 18: Estimation of the number of deaths avoided (A), years lived with disability avoided (B), and years of life gained (C) after the implementation of more stringent tobacco control policies
Such policies include increased cigarette prices, protections from environmental tobacco smoke, health warnings, and bans on tobacco advertising, promotion, and sponsorship. Data are broken down by WHO region. The appendix (pp 7–8) contains full details on the methods.

the individual smoker.[300] There are also vast differences in smoke-free legislations between and within countries, even though such legislation is beneficial to child health.[301] Understanding of exposure to e-cigarette smoke is growing, and it is now clear that vaping is harmful. Due to a lack of legislation and conflicting approaches to e-cigarette use in the medical field,[302] e-cigarettes and vapes can often be used in smoke-free areas and public confusion persists regarding their harmful effects.

Combatting tobacco use, especially among young people, will require a multipronged approach that focuses on advocacy and public education, more stringent anti-tobacco legislation, and improved enforcement of legislation. If all countries adopt

smoking bans, health warnings, and advertising bans at the strictest level, and raise cigarette prices, there could be 142 218 fewer deaths due to COPD, 725 578 fewer years of life lived with disability, and 2 419 035 life-years gained worldwide yearly (figure 18).[303] In addition to adopting new and more rigorous legislation, the medical community should be proactive in informing smokers about the benefits of smoke-free homes and smoke-free transportation. A study[304] in the Netherlands showed that only 27 (11%) of 245 physicians consistently addressed passive smoking in children and only 61 (25%) had received training on the deleterious effects of passive smoking. Patient assessments should concentrate not only on cigarette smoking but should also relate to all types of smoking (e-cigarettes, cannabis, and water-pipe smoking, and environmental exposure to tobacco smoke).

Indoor pollutants
The health effects of indoor air pollution related to indoor energy sources are substantial, and improved management of this lifelong risk factor will help to eliminate COPD. Wood-burning stoves reduce heating costs and are easily accessible, but wood smoke adversely affects respiratory health and disproportionately affects women and children in low-income settings. Global initiatives are needed to reduce the effects of this exposure. Increased public awareness will be an important factor for driving change.

Given that LMICs account for more than 80% of deaths and illness episodes related to COPD,[7] any mission to eliminate COPD globally should include strategies targeted towards these settings. Installation of kitchen chimneys and improved biomass stoves reduce the effects of indoor air pollution.[305] Improved stove and ventilation system designs also attenuate lung function decline and reduce the incidence of COPD.[306] However, several previous studies of interventions to replace biomass stoves with clean fuel (biogas or liquefied petroleum gas) stoves were unsuccessful in the long-term because of financial and infrastructure problems, low awareness, and sociocultural barriers.[307] Biomass is the most affordable fuel for domestic energy production due to its availability, and interventions to move towards cleaner fuels are not always feasible in rural communities or for those with low socioeconomic status. The FRESH AIR project has helped to identify factors that are essential to the successful implementation of health interventions in LMICs.[308] One of the key learnings from the project was that strategies need to be tailored to the local context (culturally and with awareness of regional health and political infrastructure). When fuel sources cannot be changed, improving ventilation and reducing the proximity of children to smoke within the home are key factors that can be improved via public awareness.

A study[309] showed that use of air cleaners with high-efficiency particulate air and carbon filters in the homes of former smokers with COPD was associated with reductions in indoor particulate matter concentrations in a US setting. Although the study did not reach statistical significance for the primary outcome (6-month change in scores on the St George's Respiratory Questionnaire) in the intention-to-treat analysis, portable high-efficiency particulate air cleaner use significantly improved several respiratory outcomes. Environmental interventions that improve air quality represent a potentially novel approach to reducing respiratory morbidity in patients with COPD, although larger studies are needed to confirm health benefits.

Ambient air pollution
Many organisations promote the concept that access to clean air is a right and not a privilege. In 2018, the first WHO conference on air quality and health emphasised the need to include health arguments in advocacy efforts to improve air quality globally. In 2021, WHO revised its air quality standards and declared that there are no thresholds for health effects: anything but clean air is harmful.[130] A commitment by stakeholders to effect change agreed upon by the conference has led to the development of a commitment paper in Europe signed by more than 50 medical societies and patient organisations representing different diseases.[310] The organisations committed to include air quality in their educational programmes, to ensure that clinical guidelines include specific consideration of the effects of air quality, to provide information for health-care professionals to help advise patients, to invest in research on the link between air quality and health, and to raise awareness to make reduction of air pollution a priority for all.

WHO's BreatheLife campaign encourages cities to improve air quality through multiple measures. Healthy Air is an American Lung Association (ALA) initiative that aims to improve the quality of both indoor and outdoor air by reducing vehicle idling near schools and optimising city planning of new schools, among other initiatives. The US Environmental Protection Agency (EPA), in partnership with the ALA, has designed an Indoor Air Quality Tools for Schools programme that, if widely adopted, has the potential to improve air quality for children at school.[311] As part of the Healthy Air initiative, the ALA also analyses data from official air-quality monitors and releases an annual State of the Air report that allows citizens to look up air quality in their community.

In 1970, the USA adopted the Clean Air Act, which gave the EPA the power to take action to fight environmental pollution. EPA officials then established the National Ambient Air Quality Standards (NAAQS): all states, cities, and towns in the USA have to maintain levels of pollutants beneath the thresholds set by the NAAQS or face substantial fines and penalties. From 1980 to 2015, total emissions of the major air

For **WHO's BreatheLife campaign** see https://breathelife2030.org/?

pollutants regulated by the NAAQS dropped by 63%, despite concomitant increases in the population.[312] Unfortunately, pollutant levels remain above NAAQS standards in many parts of the USA, and organisations such as the ALA continue to push the EPA to enforce stronger pollution limits and Congress to protect the Clean Air Act from those seeking to weaken clean-air protections. In many countries, including China and India, there are no governmental efforts to reduce the exponential growth in ambient air pollution and the full respiratory effects of this pollution have not yet manifested.

Particular attention should be paid to the effects of air pollution on infants and children, because air pollution impairs lung function and growth. Although the individual effect size of air pollution on lung function and growth might be small, the number of attributable cases of COPD in whom lung function is below normal within the population is very large.

The long-term effects of global warming on respiratory health are not certain. However, emerging evidence suggests that global warming could have major implications for the control of the burden of COPD, because ambient heat is closely linked to the risk of hospitalisation in patients with COPD.[313]

Occupational exposure

In the EU, exposure to chemicals in the workplace is regulated by occupational health and safety legislation and EU chemicals legislation. Employers are required to identify all chemical hazards in the workplace, to do exposure and risk assessments, and to act on the findings of these assessments. In the USA, the Occupational Safety and Health Administration within the US Department of Labor oversees respiratory health measures in the workplace. The revised Respiratory Protection Standard (1988) outlines respiratory protection standards for general, maritime, and construction industries. A revision of the Respiratory Protection Standards is due because the workforce is ageing and data for long-term acceptable levels of exposure are needed. In the absence of agreed standards, the precautionary principle to keep levels as low as reasonably achievable should be implemented.

Compounding the situation, many respiratory health-care professionals have little knowledge of, or training in, the recognition of occupational exposures or the relationship between these exposures and lung disease. Clearly, more research and education of both the public and respiratory health professionals is needed to reduce and prevent chronic lung diseases related to occupational exposures. To this end, the European Lung Foundation has developed an evidence-based digital occupational tool available in Dutch, English, French, Portuguese, and German that targets at-risk populations. The tool aims to help people to understand whether a lung problem is related to their workplace and to provide protection advice. Social media has had a major role in targeting the at-risk audience. For example, via Facebook advertising individuals tag their friends and colleagues who they believe could also be at risk. If issues arise, the person using the tool is encouraged to visit a health-care professional and talk about their work environment. To date, more than 22 000 individuals have used the tool. Around 80% of the people who used the tool came via Facebook, and roughly 50% were recommended to consult a health-care professional on the basis of their answers. More than 70% of respondents report having received no training in the workplace on protecting their lung health, and more than 90% report that they had to leave a previous job because of respiratory symptoms.

Improving predictive and diagnostic tools for early disease identification

People with COPD most commonly present with advanced disease. Yet in most people COPD has a prolonged asymptomatic phase during which preventative strategies are likely to be more effective. Therefore, screening and case-finding for COPD is a promising way forward. However, the available tools provide only a list of risk indicators—they do not quantify the risk. Furthermore, many health agencies recommend against screening. This approach is in stark contrast to that in heart disease, for which there are risk calculators based on algorithms derived by prediction models to educate the public about their risks and flag the requirement for confirmatory tests. There is a pressing need for targeted and innovative approaches to improve the prediction of COPD.

It is time to move beyond a diagnostic algorithm for COPD based solely on spirometric lung function abnormalities and to adopt a more comprehensive approach. Emphasis should be placed on early diagnosis and type-specific classification based on algorithms that capture early symptoms and biomarkers of risk, complemented by a range of pulmonary function testing and imaging (particularly CT).

In low-income settings, early diagnosis of COPD is challenging due to limited access to health care, including spirometry. Hence, interest is increasing in establishing new case-finding instruments for COPD that can be implemented in low-income settings (including use of symptoms and peak flow meters).[314] An example of a successful case-finding method implemented by WHO's acute lower respiratory infection programme was the use of respiratory rate and chest in-drawing for early diagnosis of pneumonia in children by primary health-care workers.[315] The simplification and broad deployment of this approach to early diagnosis and treatment of pneumonia have enabled substantial reductions in mortality in LMICs, where access to paediatricians is limited. Such innovative diagnostic approaches are crucial to handling the high COPD burden in low-income settings.

For the **digital occupational tool** see https://yourlungsatwork. europeanlung.org

Increased treatment efficacy and effectiveness and cure

In a survey[316] of 1102 US patients with COPD, 82% were satisfied with their treatment plan, but only 12% stated that their disease was completely controlled. Further surveys by the COPD Foundation have suggested that most patients desire treatments that have a greater effect on their symptoms or that halt disease progression.[317] The drug pipeline needs to be more robust, and there needs to be a shift of focus from blockbuster drugs aimed at most or all patients with moderate to severe disease to drugs targeting specific molecular pathways in subgroups, particularly patients with early disease. Increased public and private financial investment into the basic research necessary to identify targetable pathways among these subgroups is urgently needed, as is faster translation of these findings to the clinic. Faster translation will require testing of novel therapeutics in complex tissue models, including cell-based organoids that mimic the pathophysiology of specific COPD types, and a new approach to clinical trials whereby more homogeneous populations defined according to disease mechanism and not spirometry are enrolled.

Low availability of, inadequate health insurance coverage for, poor referral rate to, and low adherence to pulmonary rehabilitation preclude substantial effects at the population level.[318] Alternative points of access, improved training of professionals, and consensus between health-care professionals and payers on the definition of pulmonary rehabilitation could improve the situation. An American Thoracic Society taskforce has defined the essential components of a rehabilitation process, which in turn facilitates the development of novel approaches such as tele-rehabilitation.[281] Although the effects of exercise training last longer than those of respiratory pharmacotherapy, the benefits of exercise progressively diminish over time and thus maintenance programmes are essential to conserve and extend the benefits.[281]

Individual, personalised care of patients with COPD is important. It is imperative that patients are approached holistically, with a focus on individual needs, capabilities, preferences, and resources. Patients' broader living environments should also be covered in assessments. Thereafter, an individualised interdisciplinary care plan should be designed that specifically targets the priorities jointly set by the patient and their formal and informal care providers. Besides pharmacological treatment, inhalaion instruction, exacerbation management, and physical exercise, such a care programme might also include healthy lifestyle, psychological, self-management, and social care support, which are commonly not disease specific.

Eliminating disparities

A growing body of evidence shows race and gender disparities in COPD outcomes, but social and socioeconomic factors almost certainly drive most of these inequities.[31,32] WHO estimates that at least 250 million children younger than five years are in danger of poor development in LMICs due to poverty.[34] In parts of India and Africa, growth stunting affects one in three children,[319] and it will be many years before the full effects on lung health and the prevalence of COPD are understood. Although agencies such as UNICEF, WHO, the World Food Programme, and the International Fund for Agricultural Development are helping to drive global efforts to end malnutrition, the burden of the problem is massive and will require intervention at the country and regional level. Furthermore, given the racial, regional, and socioeconomic disparities in COPD outcomes,[31,32,320] individual countries will ultimately need to develop local initiatives tailored to specific regions to address differences in food access, maternal care, preventive health measures, access to primary and specialty care, and availability of pharmacological and non-pharmacological treatments.

Advancing research and development

Funding for COPD research has been disproportionately low relative to the impact of the disease for many decades, and has declined even further since the inception of this Commission. For no other chronic disease is there such a mismatch between funding and public health burden. However, efforts are underway to address this situation.

In 2017, the US National Institutes of Health launched a COPD national action plan that provided 203 grant awards by 2019. One of the grants was for the first ever lung health cohort, which will examine factors influencing lung health over the life course.[321] A cohort of patients with early COPD is also being developed in Europe and the USA. The Lung Foundation in the Netherlands has launched the Accelerate project to focus on innovative solutions for lung health, including lung regeneration. By 2023, Accelerate aims to have funded internal collaborations to fully understand lung regeneration, to have an organoid that mimics the biology of the lung, and to have begun the first clinical studies of lung stem cells that repair damaged lung tissue.

We also advocate for better funding and support for non-pharmacological interventions in COPD. Of 1685 individuals living with chronic lung disease, 1549 (92%) thought that pulmonary rehabilitation should be part of the health-care services available to all patients.[322] However, 1015 (60%) reported challenges in accessing pulmonary rehabilitation.[322] As part of the Rehabilitation 2030 initiative, WHO is building evidence-based packages for rehabilitation that should foster global expansion of access for all patients with COPD.[323]

When calling for the development of innovative treatment options, we acknowledge that the health system is given finite resources. Money can be spent only once, and spending it on a new treatment could displace treatment (and thus benefits) elsewhere in the system.

Therefore, payers require evidence of cost-effectiveness before taking the decision to reimburse a new treatment. Development of personalised and precision medicine in COPD means that new treatments will probably be suitable only in target subgroups of patients, which will cause treatment costs to go up. The cost-effectiveness of these new treatments might therefore be difficult to prove.

The cost-effectiveness of interventions in COPD is generally estimated with health economic models. In the past, these models were mainly Markov models in which COPD severity was classified on the basis of airflow limitation only, and COPD exacerbation frequencies, costs, and utilities were then assigned to these severity states. These models generate only a few outcome measures, including lung function decline, exacerbation frequency, quality-adjusted life-years, and costs. Pharmaceutical companies, academics, and consultants have each constructed their own models, which makes comparison of results challenging. As treatments are increasingly personalised, comprehensive patient-level simulation models that include many patient and disease characteristics, comorbidities, and a greater diversity of outcomes are needed. In one patient-level simulation model of this type, the cost-effectiveness of interventions that reduced lung function decline, increased time to a COPD exacerbation, improved physical activity, and reduced the probability of having symptoms was compared.[324] Although the model is based on data from more than 35 000 people with COPD, all the data come from one pharmaceutical company. What is really needed to inform decision makers is an open-access core model of COPD that allows estimation of the cost-effectiveness of many different interventions with the same model across datasets.

People-centred integrated care models, especially for vulnerable people with multimorbidities, aim to improve outcomes beyond health, including wellbeing (eg, social relationships and participation, resilience, enjoyment of life, autonomy) and experience with care (eg, continuity of care, person-centredness, feeling safe). Such outcomes are not captured by quality-adjusted life-years, so there is

	Practical goals
Prohibit all kinds of smoking including—but not restricted to—cigarette smoking, water-pipe smoking, e-cigarette smoking (vaping), cannabis smoking, and smoking of other combustible substances	50% of countries to ban smoking by 2035
Eliminate environmental exposures to anything but clean air, including indoor and outdoor pollution, wildfire smoke, and occupational exposures to toxic fumes and gasses; regulatory authorities should strengthen legislation governing acceptable levels of exposure to inhalable particulate matter and ozone	50% of countries to introduce annual limits (lower than those recommended by WHO) for exposure to inhalable particulate matter <2·5 μm in diameter, particulate matter <10 μm in diameter, and ozone
Support measures associated with improved and sustained general health, including reductions in global poverty and improvements in nutrition, vaccination, prenatal care, physical activity, and mental health	At least a 50% reduction in people living below the poverty-line by 2035; all countries should provide free vaccinations and mobilise educational campaigns to inform at-risk individuals; free or low-cost health care for all
Diagnose COPD based on expanded criteria, including the presence of respiratory symptoms, personal history of risk factors, and persistent airflow limitation or ventilatory heterogeneity (as assessed by spirometry, other pulmonary function testing, or CT)	By 2035, the proportion of patients diagnosed with mild spirometric airflow obstruction should increase to at least 50% of the total
Research and development should focus on treatment of early disease	By 2030, 75% of published clinical trials should be focused on patients with early or mild disease
COPD should be classified into one of five types on the basis of the predominant risk factor present to increase awareness of risk factors, improve detection of people with non-smoking-related COPD and those with early disease, and foster research into therapies targeting specific disease mechanisms	COPD diagnosis by type should be included in the *International Classification of Diseases* coding system By 2035, at least one specific pharmacological or non-pharmacological therapy should be approved for each type of COPD
Diagnosis of exacerbations should be based on a standard assessment confirmed by evidence of worsening airflow limitation or ventilatory heterogeneity, airways or systemic inflammation, or lung infection in a patient with increased respiratory symptoms (after exclusion of other disorders that mimic this presentation)	Exacerbation frequency should be similar worldwide by 2035 as a result of the establishment of a standard definition and assessment
Effective pharmacological and non-pharmacological therapies should be made available worldwide; development of new therapies should focus on underlying pathophysiology and take into account disease heterogeneity (including COPD type)	By 2035, at least 80% of patients with COPD should have disease control, as evidenced by the absence of respiratory symptoms and exacerbations and normal or near-normal quality of life, exercise capacity, and life expectancy
Definitions of treatment effectiveness should take patient-reported outcomes into account	By 2030, 75% of studies should include a patient-centred outcome as a primary outcome
Regulatory agencies should regularly revisit and update endpoints for clinical trials of treatments for different COPD types	By 2035, 75% of new therapies should be approved on the basis of non-spirometric criteria
Funding agencies should increase financial investments to adapt to the worldwide burden of COPD	By 2030, the total public and private global research and development expenditures for COPD should increase by 50%

COPD=chronic obstructive pulmonary disease.

Table 8: Recommendations for the elimination of COPD

a need to broaden the assessment framework and explore the potential of multi-criteria decision analyses,[325] which combine measurement of a broader set of benefits with the weighting of these benefits to generate a single overall score that allows promotion of an economy of wellbeing.

Conclusions and recommendations

It is quite possible that the elimination of COPD is not achievable, much as it might be impossible to eliminate other highly complex diseases with high morbidity and mortality, such as cancer, heart disease, and diabetes. However, our approach to date has lacked clarity, focus, and urgency and the global burden of COPD continues to increase. Although the decline in tobacco smoking in high-income countries is welcome, failure to control other risk factors jeopardises the gains that might ultimately be realised. In this Commission, we have attempted to reset the conversation about COPD to emphasise the importance of non-tobacco risk factors and primary prevention and the need to promote lung health across the life course beginning at conception, to improve disease classification and expand tools for diagnosis, and to develop better treatments aimed primarily at reversal and cure. Table 8 details our urgent recommendations to help drive transformational change and to assess progress along this new path towards the elimination of COPD. We are committed to tracking this progress, and ask the respiratory community to join us.

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