Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/202631878

The Role of Emergency Professionals, Nurses and Public Health Professionals in Managing Acute Exacerbations of Chronic Obstructive Pulmonary Disease.

Hassan Jaber Hassan Ammash[(1)] , Hamzah Shuwaier Ali Salwa[(2)] , Mohammed Muthker M Almutairi[(3)] , Abdullah Msfer Saad Alosaimi[(4)] , Hani Muqaybil Alruwaili[(5)] , Atallah Zafran Altarfawi[(6)] , Hussain Hassan H Abushaqarah[(7)] , Talal Ali Alsharari[(8)] , Abdulrahman Abdulaziz Awad Al-Otaibi[(9)] , Mansour Ibrahim Ahmed Otudi[(10)] , Khaled Jumaan Khaled Alghamdi[(11)] , Ahlam Mohammed Jaradi Tayran[(12)]

(1)Saudi Red Crescent Authority, Saudi Arabia, Saudi Arabia
(2)Crisis and Disaster Management Center – Jazan, Ministry of Health, Saudi Arabia, Saudi Arabia
(3)Medical Rehabilitation Hospital – Madinah, Ministry of Health, Saudi Arabia, Saudi Arabia
(4)Ministry of Health Branch – Riyadh Region, Ministry of Health, Saudi Arabia, Saudi Arabia
(5)Turaif Center – Third Sector – Northern Borders, Saudi Red Crescent Authority, Saudi Arabia, Saudi Arabia
(6)Turaif Center – Third Sector – Northern Borders, Saudi Red Crescent Authority, Saudi Arabia, Saudi Arabia
(7)Emergency and Disaster Management Department – Jazan Health Cluster, Ministry of Health, Saudi Arabia, Saudi Arabia
(8)Al-Jawf Branch – Sector Four, Saudi Red Crescent Authority, Saudi Arabia, Saudi Arabia
(9)Not Provided, Ministry of Health, Saudi Arabia, Saudi Arabia
(10)Crisis and Disaster Center – Jazan Health Cluster, Ministry of Health, Saudi Arabia, Saudi Arabia
(11)King Abdulaziz University Dental Hospital – Jeddah, Ministry of Education, Saudi Arabia, Saudi Arabia
(12)Jazan Health Cluster, Ministry of Health, Saudi Arabia, Saudi Arabia

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder characterized by persistent airflow limitation, chronic inflammation, and progressive respiratory impairment. Its clinical presentation and progression vary considerably among patients, creating challenges for diagnosis, treatment selection, and long-term disease control. Emerging evidence supports personalized approaches that address pulmonary and extrapulmonary disease characteristics.

Aim: This review examines recent developments in COPD assessment and management, with particular emphasis on treatable traits, biological therapies, smoking cessation, pulmonary rehabilitation, oxygen therapy, and associated comorbidities.

Methods: A narrative review approach was used to discuss evidence concerning COPD pathophysiology, diagnostic investigations, emerging therapeutic strategies, and multidisciplinary management. Particular attention was given to clinical trials investigating targeted biological agents and interventions addressing modifiable disease characteristics.

Results: COPD assessment increasingly incorporates spirometry, imaging, inflammatory biomarkers, and functional investigations to identify disease phenotypes and support earlier diagnosis. The treatable traits approach provides a personalized framework for managing pulmonary, extrapulmonary, and behavioral factors, including its potential application in pre-COPD. Among biological therapies, dupilumab has demonstrated reductions in moderate or severe exacerbations and improvements in lung function among patients with elevated blood eosinophils. Evidence supporting IL-5 and TSLP pathway inhibitors remains inconsistent, while IL-33-targeted therapies require further investigation. Smoking cessation, pulmonary rehabilitation, and appropriate oxygen therapy remain essential management strategies. Cardiovascular disease, sleep-disordered breathing, obesity, and dysfunctional breathing also require systematic assessment because they influence clinical outcomes and disease burden.

Conclusion: COPD management is evolving toward personalized, multidimensional care. Integrating early diagnosis, treatable traits, targeted therapies, lifestyle interventions, and comorbidity management may improve treatment selection and patient outcomes.

Keywords: Chronic obstructive pulmonary disease; treatable traits; biological therapy; smoking cessation; pulmonary rehabilitation; comorbidities.

IntroductionChronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by persistent airflow limitation, chronic respiratory symptoms, and progressive structural changes in the lungs. It represents a major cause of morbidity and mortality worldwide and places a substantial burden on healthcare systems. Over the past three decades, COPD ranked as the third leading cause of death globally before declining to fourth place in 2021, partly due to the impact of COVID-19.

*Corresponding author ammash1234@icloud.com (Hassan Jaber Hassan Ammash).
Receive Date: 5 September 2026, Revise Date: 30 October 2026, Accept Date: 18 November 2026

Mortality rates remain particularly high in South Asia, Southeast Asia, East Asia, and Oceania, reflecting differences in exposure to respiratory risk factors, access to healthcare, and disease management [1]. The economic consequences of COPD extend beyond direct medical expenditure. Patients frequently require repeated consultations, hospital admissions, long-term medication, oxygen therapy, and pulmonary rehabilitation. Disease-related disability can also reduce employment opportunities and productivity while increasing the caregiving burden on families. In the United States, annual medical expenditure among patients with COPD was approximately 2.5 times higher than that among individuals without the disease. COPD-attributable healthcare costs reached an estimated 25.3 billion US dollars in 2019, equivalent to approximately 1,445 dollars per patient, with projections reaching 60.5 billion dollars by 2029. These estimates do not fully account for indirect costs associated with disability and lost productivity [2]. COPD develops through complex interactions between genetic susceptibility, environmental exposures, airway inflammation, and structural lung damage. Although cigarette smoking remains a major risk factor, exposure to biomass fuels, ambient air pollution, occupational dust, and chemical irritants also contributes to disease development. These exposures are particularly relevant in low- and middle-income countries, where many patients develop COPD without a history of tobacco smoking.

Timely diagnosis and individualized treatment are essential for improving clinical outcomes. Diagnostic assessment commonly involves spirometry, clinical evaluation, exposure history, and investigation of relevant comorbidities. Screening strategies based on structured questionnaires, either alone or combined with spirometry, may offer cost-effective approaches to identifying individuals with undiagnosed disease [3,4]. COPD management requires an integrated approach that addresses both pulmonary impairment and associated systemic complications. Pharmacological interventions include bronchodilators, inhaled corticosteroids in selected patients, and other therapies according to symptoms, exacerbation history, and inflammatory characteristics. Non-pharmacological strategies include smoking cessation, vaccination, physical activity, pulmonary rehabilitation, nutritional support, and reduction of environmental exposures. This review examines recent evidence concerning COPD pathophysiology, non-smoking-related disease, airway inflammation, molecular endotypes, diagnostic approaches, and multimodal management. Particular attention is given to emerging mechanisms that may support more precise treatment strategies and improve long-term disease outcomes.

Non-Smoking COPD:

Although cigarette smoking is an established risk factor for chronic obstructive pulmonary disease (COPD), a substantial proportion of patients develop the condition without a history of tobacco use. This pattern is particularly evident in low- and middle-income countries (LMICs), where approximately 30%–40% of COPD cases may be unrelated to smoking. Biomass fuel combustion, indoor air pollution, occupational exposures, and ambient particulate matter are important contributors. Women are disproportionately affected in several regions because of prolonged exposure to smoke generated by cooking and heating fuels [5]. Evidence from a systematic review and meta-analysis involving nearly 500,000 participants in China demonstrated that 41.1% of patients with COPD had never smoked. The proportion was considerably higher among women than men, reaching 81.3% and 22.3%, respectively. Biomass fuel exposure was also associated with COPD among never-smokers, with an odds ratio of 1.25 (95% CI: 1.06–1.44) [6]. Findings from India similarly identified biomass fuel exposure as an important risk factor, particularly among women [7]. Ambient and household air pollution contribute to respiratory disease through prolonged exposure to inhaled particles and chemical pollutants. Approximately 7.3 billion people worldwide are exposed to unsafe annual concentrations of particulate matter with a diameter of 2.5 μm or less (PM2.5), with approximately 80% living in LMICs [8]. Because of their small size, PM2.5 particles can penetrate deep into the respiratory tract and reach the small airways and alveoli. Their chemical composition and oxidative activity may trigger epithelial injury, inflammatory responses, and progressive structural damage [9]. Long-term exposure has also been associated with increased mortality. Pooled analyses from the Canadian MAPLE, US Medicare, and European ELAPSE cohorts estimated a hazard ratio of approximately 1.04 for all-cause mortality for every 5 μg/m³ increase in PM2.5 concentration [10].

Air pollution also affects small airway function, which may deteriorate before conventional spirometric abnormalities become apparent. Forced expiratory flow between 25% and 75% of forced vital capacity (FEF25%–75%) is commonly used to assess small airway dysfunction. However, its interpretation is limited by variability and dependence on forced vital capacity. Respiratory oscillometry provides an additional approach for evaluating peripheral airway abnormalities. Exposure to PM2.5, PM10, nitrogen dioxide, sulfur dioxide, and carbon monoxide has been associated with reduced FEF25%–75% and evidence of small airway dysfunction. Changes in annual pollution concentrations have also been correlated with alterations in small airway measurements [11,12]. Several molecular mechanisms may explain the relationship between air

pollution and COPD. Experimental studies have demonstrated that PM2.5 can activate the interleukin-4/signal transducer and activator of transcription 6 (IL-4/STAT6) pathway, promoting M2 macrophage polarization and matrix metalloproteinase-12 expression. These changes may impair the alveolar epithelial barrier and accelerate extracellular matrix degradation [16]. Other studies have linked PM2.5 exposure to airway remodeling through collagen-I and alpha-smooth muscle actin expression, involving autophagy-related GATA4/TRAF6/NF-κB signaling [17]. Biomass-derived particles may also promote fibroblast-to-myofibroblast transition through PI3K/AKT/TRPC1 signaling [18]. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is another important regulator of pulmonary antioxidant and anti-inflammatory responses [13–15,19]. These findings indicate that non-smoking COPD involves distinct environmental and molecular mechanisms. Understanding these pathways may support preventive strategies and the development of targeted treatments that address pollution-related airway injury and disease progression.

Airway Inflammation and COPD Endotypes:

Chronic obstructive pulmonary disease (COPD) is a heterogeneous inflammatory disorder involving persistent immune activation, airway remodeling, and destruction of pulmonary tissue. Its pathological changes primarily affect two anatomical regions. The small airways develop peribronchovascular inflammation, fibrosis, and narrowing, whereas the alveoli undergo progressive wall destruction, resulting in emphysematous changes. The relative contribution of these processes differs between patients and contributes to variation in clinical presentation, disease progression, and treatment response. COPD encompasses several clinical phenotypes, including smoking-related and non-smoking-related disease, predominant breathlessness, chronic productive cough, and frequent or infrequent exacerbations. Although these classifications help describe clinical characteristics, they do not always identify the underlying molecular mechanisms responsible for disease progression. Consequently, increasing attention has been directed toward identifying biological endotypes that can provide a more accurate basis for individualized treatment. Genetic susceptibility contributes to COPD development in selected populations. Alpha-1 antitrypsin deficiency (AATD) is an established inherited risk factor associated with premature emphysema, particularly among individuals with additional environmental exposures. Telomere-related genetic variations have also been associated with susceptibility to pulmonary disease [20]. Identification of AATD is clinically important because selected patients may benefit from augmentation therapy, which has demonstrated survival benefits in appropriate populations [21].

The inflammatory response in COPD involves multiple immune and structural cell populations. Neutrophils, macrophages, and eosinophils contribute to airway inflammation, while CD4+ and CD8+ T lymphocytes, monocytes, mast cells, and innate lymphoid cells also participate in disease-related immune activity [22]. Airway epithelial cells, endothelial cells, and fibroblasts further influence inflammation through the release of cytokines, chemokines, and other signaling molecules. Interactions among these cells contribute to mucus hypersecretion, airway remodeling, small airway obstruction, and alveolar destruction [20,23,24]. Blood eosinophil counts are widely used as a biomarker in COPD management. They can help estimate the likelihood of exacerbations and predict the potential response to inhaled corticosteroids (ICS), particularly when considered alongside clinical history [25]. However, the concept of eosinophilic COPD requires further clarification. Evidence suggests that eosinophils in COPD may differ biologically from those observed in asthma. A comparative study identified inflammatory eosinophils (iEos) as more abundant in asthma than in COPD, regardless of total eosinophil counts. These cells also expressed higher levels of interleukin-5 receptors than resident eosinophils. In COPD, iEos numbers were not associated with ICS use, disease severity, or exacerbation frequency [26]. These findings suggest that eosinophil biology in COPD cannot be fully explained by blood eosinophil counts alone. Multi-omics technologies have expanded the understanding of molecular variation in COPD. Proteomic, transcriptomic, and lipidomic analyses have identified the involvement of IL-33, tumor necrosis factor-alpha, and interferon-gamma in eosinophil activation among patients with COPD and asthma-COPD overlap [27]. Airway epithelial transcriptomic studies have also demonstrated type 2 inflammatory signatures, IL-13 expression, and mast cell activation in patients with airway eosinophilia. ICS treatment was associated with a reduction in this inflammatory signature [28]. Integrating multi-omics datasets with machine learning has created opportunities to identify distinct COPD endotypes. These approaches may reveal molecular differences among patients who share similar clinical characteristics but have different inflammatory and structural disease mechanisms [29–31]. Ultimately, endotype identification may support precision medicine by improving patient classification and guiding the selection of targeted therapies.

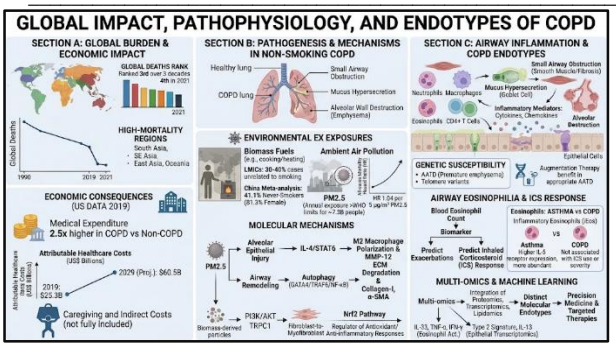


Figure-1: COPD Overview.

Investigations in COPD

The diagnosis and assessment of chronic obstructive pulmonary disease (COPD) require a combination of clinical evaluation, pulmonary function testing, imaging, and selected biomarkers. Early identification is important because structural and functional lung abnormalities may develop before conventional spirometric criteria confirm persistent airflow obstruction. Although spirometry remains the primary diagnostic investigation, its limitations have encouraged the development of additional approaches for identifying early disease, assessing small airway abnormalities, and predicting clinical progression.

Spirometry and Early Identification

COPD should be suspected in individuals with respiratory symptoms, such as chronic cough, sputum production, and dyspnea, particularly when relevant risk factors are present. Diagnosis is generally confirmed by post-bronchodilator spirometry demonstrating a forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio below 0.70. However, some guidelines recommend interpreting the ratio against its lower limit of normal (LLN), because the FEV1/FVC ratio physiologically decreases with age. Using a fixed threshold may therefore result in underdiagnosis among younger adults and overdiagnosis among older individuals [32]. Preserved Ratio Impaired Spirometry (PRISm) has emerged as an important spirometric pattern for identifying individuals who may be at risk of developing COPD. It is characterized by an FEV1/FVC ratio of at least 0.70 alongside an abnormal FEV1 below 80% of the predicted value. Analysis of the US National Health and Nutrition Examination Survey data from 2007–2012 estimated PRISm prevalence at 9.6%–10.2%, compared with COPD prevalence of 13.1%–14.3%. PRISm was more frequently observed among females [33]. Longitudinal studies have demonstrated the potential value of alternative spirometric thresholds. The Tasmanian Longitudinal Health Study evaluated pre-bronchodilator FEV1/FVC Z-scores in participants followed from 45 to 53 years of age. Individuals with values below the 10th percentile had a 36-fold higher risk of developing COPD over eight years. The approach demonstrated 88% sensitivity and 87% specificity [34]. Similarly, the BOLD cohort, involving 30,757 participants with a median follow-up of 8.4 years, found that a pre-bronchodilator FEV1/FVC Z-score threshold below the ninth percentile could facilitate early identification of airflow obstruction, particularly among current smokers [35]. The clinical importance of PRISm was further demonstrated by the Nagahama study. Approximately 53% of individuals with PRISm initially reported respiratory symptoms, particularly dyspnea, while 39% of initially asymptomatic participants developed symptoms within five years. PRISm was independently associated with subsequent COPD development, regardless of smoking history or comorbidities [36]. Spirometry also provides prognostic information. Studies have associated an FEV1/FVC ratio below 0.70 with reduced remaining life expectancy among symptomatic former smokers and non-smokers, supporting its relevance beyond diagnosis [37].

Quantitative Computed Tomography

Quantitative thoracic computed tomography (CT) provides information about structural lung abnormalities that may not be detected through conventional spirometry. It can identify emphysema, air trapping, small airway disease, airway wall thickening, and mucus plugging. These findings are particularly relevant in individuals with respiratory symptoms or substantial exposure histories despite preserved spirometric measurements. The BEACON cohort investigated young smokers with preserved lung function, defined by FEV1 above 80% of the predicted value. Participants had a median age of 39 years and an average smoking history of 16 pack-years. CT imaging demonstrated air trapping, emphysematous changes, and abnormalities involving lung parenchyma and pulmonary vasculature. These abnormalities were associated with accelerated subsequent FEV1 decline, suggesting that structural lung injury may precede conventional spirometric evidence of COPD [38]. Artificial intelligence has further expanded the potential applications of CT imaging. Generative AI approaches have demonstrated the ability to assess small airway disease from a single inspiratory CT scan, with measurements showing significant associations with subsequent deterioration in FEV1 [39]. Quantitative CT can also characterize mucus pathology using several parameters, including mucus plug score, total airway count (TAC), and percentage airway wall area (WA%). The mucus plug score represents the number of bronchopulmonary segments containing completely occluded mucus plugs [40,41]. Mucus plugging may remain clinically unrecognized. Approximately one-third of smokers with COPD and high CT mucus scores report mucus-related symptoms, while another third of patients without cough or sputum production demonstrate mucus plugs on imaging. Older age, female sex, and

Black race have been identified as factors associated with clinically silent mucus plugging [42,43]. A higher mucus plug score is associated with greater dyspnea, increased exacerbation risk, oxygen desaturation, reduced FEV1, lower TAC, thicker airway walls, more extensive emphysema, and increased mortality [42–46].

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (MRI) provides an additional approach for evaluating pulmonary structure and function without exposing patients to ionizing radiation. It can assess regional ventilation, alveolar dimensions, and gas exchange. Hyperpolarized xenon-129 MRI enables measurement of ventilation defect percentage (VDP), which is a sensitive indicator of regional ventilation abnormalities and small airway disease [47]. Alveolar airspace dimensions can be quantified using the apparent diffusion coefficient (ADC) and mean diffusive length scale (LmD). These measurements provide information about structural changes associated with emphysema and alveolar destruction [48]. Dissolved-phase xenon imaging can also evaluate pulmonary gas exchange, offering insight into functional impairment beyond conventional pulmonary function measurements [49]. Despite these advantages, functional MRI remains limited by cost, availability, and the need for specialized equipment and expertise. Its use is therefore more appropriate in selected clinical and research settings.

Mucus Characteristics and Emerging Biomarkers

Mucus plugging is increasingly recognized as a potentially treatable COPD characteristic because it contributes to airway obstruction and may influence disease progression. Multi-omics approaches combining microbiome analysis with biochemical and biophysical assessment of airway mucus may help identify distinct disease patterns. A study using shotgun metagenomic sequencing found increased concentrations of MUC5AC and MUC5B mucins and associations involving Achromobacter and Klebsiella among patients experiencing accelerated lung function decline [50]. These findings suggest that mucus composition and airway microbial communities may contribute to disease heterogeneity. Biomarkers are also being investigated to improve COPD endotyping and treatment selection. Blood eosinophil counts are commonly used to estimate the likelihood of response to inhaled corticosteroids and certain targeted therapies. However, their interpretation is affected by diurnal variation and limited specificity [51]. Fractional exhaled nitric oxide (FeNO), which primarily reflects IL-13-mediated type 2 inflammation, has demonstrated greater temporal stability in patients with stable COPD [52]. Nevertheless, the predictive value of FeNO for biologic treatment response remains uncertain. The BOREAS and NOTUS trials evaluated dupilumab in patients with COPD and demonstrated clinical benefits across baseline FeNO categories, including values above and below 20 parts per billion [53,54]. These findings indicate that FeNO should not currently be considered a standalone predictor of response in eosinophilic COPD. Overall, COPD investigations are moving toward an integrated approach that combines spirometry, quantitative imaging, functional MRI, and molecular biomarkers. Spirometry remains essential for confirming airflow obstruction, while advanced imaging can identify structural abnormalities and characterize treatable traits. Further validation of biomarkers and imaging techniques is needed before their widespread implementation in routine clinical practice.

The Treatable Traits Approach in COPD

The treatable traits (TT) approach represents a shift from the traditional one-size-fits-all model toward personalized, multidimensional care in chronic obstructive pulmonary disease (COPD). Rather than classifying patients solely according to airflow limitation or disease severity, this model identifies clinically relevant, measurable, and modifiable characteristics that contribute to individual disease manifestations. These traits are grouped into three main domains: pulmonary, extrapulmonary, and behavioral or lifestyle-related factors [55]. However, identifying these traits alone is insufficient. Their clinical value depends on integrating appropriate biomarkers and diagnostic measures that reflect the underlying pathophysiological processes in each patient. Within the pulmonary domain, treatable traits may include persistent airflow obstruction, airway inflammation, mucus hypersecretion, emphysema, and frequent exacerbations. Extrapulmonary traits include cardiovascular disease, osteoporosis, muscle dysfunction, anxiety, depression, and nutritional abnormalities. Behavioral and lifestyle factors encompass smoking, physical inactivity, poor inhaler technique, and environmental exposures. Identifying these components allows clinicians to select interventions according to individual needs rather than applying uniform treatment strategies. Evidence suggests that this personalized approach can improve health-related quality of life, reduce hospital admissions, and enhance treatment precision in patients with respiratory diseases, including COPD [56].

The TT framework also supports comprehensive management, combining established interventions, such as appropriate inhaled pharmacotherapy, smoking cessation, pulmonary rehabilitation, and vaccination, with selected advanced treatments. These may include targeted lung denervation in appropriately selected patients [57,58]. Effective implementation requires coordination among respiratory specialists, primary care physicians, nurses, pharmacists, and rehabilitation professionals to address pulmonary and non-pulmonary needs. An important development is the extension of the TT approach to pre-COPD,

enabling clinicians to identify individuals at increased risk before persistent airflow limitation develops. This preventive strategy considers interactions between genetic susceptibility and environmental exposures throughout life. Potential treatable traits include respiratory symptoms, structural or physiological lung abnormalities, obesity, physical inactivity, smoking, and occupational or environmental exposures [59]. Applying this framework across the COPD spectrum may facilitate earlier intervention, improve risk assessment, and support personalized preventive and therapeutic strategies.

COPD Treatment

Biological Therapy in COPD

Biological therapies are being investigated as targeted treatments for selected patients with COPD, particularly those with evidence of type 2 inflammation and elevated blood eosinophils. However, clinical responses vary according to the biological pathway targeted and patient selection. Mepolizumab and benralizumab target the IL-5 pathway but have not demonstrated consistent reductions in COPD exacerbations. In METREX, mepolizumab produced an 18% reduction in annual exacerbations among patients with elevated eosinophils, although the overall population did not achieve a significant benefit. METREO also failed to demonstrate statistically significant reductions at either the 100-mg or 300-mg dose [60]. Similarly, the GALATHEA and TERRANOVA trials did not establish significant reductions in exacerbations with benralizumab [61]. Despite these clinical findings, mechanistic investigations confirmed reductions in blood and sputum eosinophils following benralizumab administration [62]. The phase 2 ABRA trial further suggested that benralizumab may reduce treatment failure during acute exacerbations in patients with eosinophilic airway disease [63]. Further phase 3 investigations are evaluating both agents in populations selected according to blood eosinophil counts. Dupilumab, which inhibits IL-4 and IL-13 signaling through IL-4 receptor alpha, has demonstrated more consistent clinical benefits. The BOREAS and NOTUS trials showed that dupilumab, administered at 300 mg subcutaneously every two weeks, reduced moderate or severe exacerbations and improved lung function in patients with blood eosinophils ≥300 cells/μL [53,54]. Improvements in FEV1 appeared early and persisted throughout treatment. Although pooled analyses did not demonstrate a statistically significant reduction in severe exacerbations, improvements in respiratory symptoms and lung function support its potential role in selected patients [64]. Tezepelumab, an anti-TSLP antibody, did not meet the primary endpoint in the COURSE trial. However, a potential benefit was observed among patients with eosinophils ≥150 cells/μL, indicating the importance of identifying responsive subgroups [65]. Other investigations targeting IL-33 pathways, including itepekimab, astegolimab, and tozorakimab, have produced mixed findings. Some subgroup analyses suggested benefits, particularly among former smokers and frequent exacerbators, but overall efficacy remains unconfirmed [66–68].

Smoking Cessation

Smoking cessation remains a central component of COPD management because it reduces mortality risk, slows lung function decline, and improves respiratory symptoms [69]. Pharmacological treatment should be selected according to smoking behaviour, previous treatment response, and individual characteristics. The nicotine metabolite ratio (NMR), which reflects CYP2A6 activity through the relationship between cotinine and trans-3-hydroxycotinine, may help guide treatment selection [70]. Varenicline has demonstrated greater efficacy than bupropion in normal NMR metabolizers, whereas bupropion may provide comparable outcomes with fewer adverse effects in slow metabolizers [71]. Patients who do not achieve abstinence with initial treatment may benefit from dose adjustment or switching therapies. Higher-dose varenicline has improved cessation outcomes in some previous non-responders, while patients who fail combination nicotine replacement therapy may benefit from dose escalation or switching to varenicline [72]. Cytisine, a plant-derived partial agonist of nicotinic acetylcholine receptors, has also demonstrated efficacy compared with usual care and nicotine replacement therapy. However, direct comparisons with varenicline remain limited [73–75]. Although electronic cigarettes have been proposed as smoking cessation tools, their ability to achieve complete nicotine abstinence remains uncertain. Continued nicotine dependence and potential pulmonary toxicity, airway inflammation, epithelial damage, and impaired mucociliary clearance raise concerns about their long-term use [76,77]. Varenicline may also support vaping cessation, highlighting the need to address both tobacco and electronic nicotine dependence [78,79].

Mood Disorder Management

Depression and anxiety frequently coexist with COPD and can influence symptom severity, treatment adherence, and quality of life. Evidence from bidirectional Mendelian randomization suggests that depression may contribute to COPD-related morbidity [80]. Negative emotional states can increase the perceived intensity of dyspnea, while breathlessness may trigger anxiety and panic, creating a cycle that worsens psychological and respiratory symptoms [81]. Patient education, psychological support, breathing strategies, and structured self-management can help interrupt this cycle [82]. Pharmacological treatment specifically targeting breathlessness remains limited. The

BETTER-B trial found that mirtazapine did not significantly improve severe breathlessness compared with placebo [83].

Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) improves exercise capacity, reduces dyspnea, and enhances quality of life through structured exercise and education. Its benefits are attributed partly to improved oxygen utilization, skeletal muscle function, and respiratory efficiency. In patients recovering from acute COPD exacerbations, PR can reduce hospital readmissions and improve submaximal exercise performance [84]. An eight-week programme has also demonstrated reductions in cardiovascular risk among former smokers with stable COPD [85]. PR remains relevant following bronchoscopic lung volume reduction using endobronchial valves (BLVR-EBV). Although a randomized trial reported only modest improvements in exercise endurance when PR followed BLVR-EBV, this does not diminish its clinical importance. Continued rehabilitation may help maintain functional gains and should remain part of post-procedural care [86,87].

Long-Term Domiciliary Oxygen Therapy

Long-term domiciliary oxygen therapy (LTDOT), generally prescribed for more than 15 hours daily, improves survival in patients with severe resting hypoxemia, particularly those with PaO2 ≤55 mmHg. However, established survival benefits have not been demonstrated consistently in patients with mild-to-moderate hypoxemia or isolated nocturnal desaturation [88]. A post hoc analysis suggested a possible survival advantage among patients who developed early exertional desaturation, defined as oxygen saturation below 88% within the first minute of the six-minute walk test. Although survival was higher among oxygen-treated patients, these findings require cautious interpretation because the analysis was not originally designed to evaluate this subgroup. Prospective controlled studies are needed before extending oxygen therapy recommendations to patients with early exertional desaturation [89].

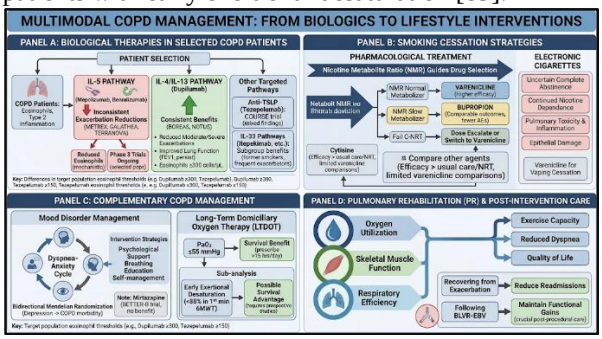


Figure-2: Treatment and Management of COPD.

Comorbidities in COPD

COPD is a systemic inflammatory disorder with clinical consequences extending beyond the respiratory system. Persistent inflammation contributes to the development of several comorbidities, particularly cardiovascular diseases, sleep-related breathing disorders, obesity, and dysfunctional breathing. These conditions influence disease progression, exacerbation frequency, functional capacity, and mortality, making their identification an essential component of comprehensive COPD management. Cardiovascular diseases are among the most important comorbidities in COPD. Systemic inflammation and shared risk factors contribute to increased susceptibility to ischemic heart disease, heart failure, and stroke. This association occurs across different COPD phenotypes, including chronic bronchitis, emphysema, and combined disease. Reported odds ratios for cardiovascular disease were 1.76, 2.31, and 2.98, respectively, compared with individuals without COPD [90]. The particularly elevated risk among patients with combined phenotypes suggests that multiple inflammatory and physiological mechanisms may contribute to cardiovascular complications [91]. Cardiovascular screening is therefore important, although overlapping symptoms, such as fatigue and breathlessness, may complicate diagnosis.

Sleep-disordered breathing represents another clinically relevant comorbidity. Obstructive sleep apnea (OSA) affects approximately 32% of patients with COPD and is associated with obesity and severe acute exacerbations. Isolated nocturnal hypoxemia occurs in approximately 27% of patients and is associated with reduced FEV1 and lower resting oxygen saturation. COPD–OSA overlap syndrome is particularly concerning because it is associated with increased exacerbation frequency and mortality, with a reported hazard ratio of 1.74 [92]. Overnight oxygen saturation monitoring and polysomnography should therefore be considered in patients with suspected sleep-disordered breathing, particularly those with obesity or recurrent exacerbations. Obesity and physical inactivity also influence respiratory function and long-term outcomes. Higher body mass index (BMI), particularly when established during early adulthood, is associated with lower FEV1 and forced vital capacity (FVC). In women, increased BMI is also associated with a reduced FEV1/FVC ratio, suggesting a relationship with airflow obstruction. Conversely, regular physical activity is associated with better lung function [93]. Weight management and exercise promotion may therefore contribute to reducing respiratory impairment and future COPD burden [94]. Dysfunctional breathing, also known as breathing pattern disorder, is an under-recognized condition that may aggravate breathlessness in COPD. It includes abnormal respiratory patterns such as hyperventilation, frequent sighing, upper thoracic breathing, and respiratory asynchrony. These abnormalities may occur together and contribute to breathlessness disproportionate to measured pulmonary impairment [95]. Using the Nijmegen Questionnaire, one cohort study identified

dysfunctional breathing in nearly 50% of COPD patients attending a tertiary care teaching clinic [96,97]. Recognizing this condition may support targeted breathing retraining and other non-pharmacological interventions as part of personalized COPD care.

Conclusion:

COPD requires an integrated management strategy that addresses its clinical heterogeneity and systemic consequences. Advances in diagnostic investigations and the treatable traits approach provide opportunities to identify individual disease characteristics and initiate targeted interventions, including during the pre-COPD stage. Biological therapies, particularly dupilumab, have expanded treatment options for selected patients with eosinophilic inflammation, although further evidence is needed for other targeted agents. Smoking cessation, pulmonary rehabilitation, and appropriate oxygen therapy remain essential components of long-term care. Equally important is the recognition and management of cardiovascular disease, sleep-disordered breathing, obesity, and dysfunctional breathing. Future research should prioritize biomarker-guided treatment selection, early intervention, and long-term evaluation of emerging therapies. A multidisciplinary, patient-centred approach offers the best framework for improving disease control, reducing exacerbations, and maintaining quality of life.

References:

1.“Global Burden of 288 Causes of Death and Life Expectancy Decomposition in 204 Countries and Territories and 811 Subnational Locations, 1990-2021: A Systematic Analysis for the Global Burden of Disease Study 2021,” Lancet 403 (2024): 2100–2132.

2. Mannino D. M., Roberts M. H., Mapel D. W., et al., “National and Local Direct Medical Cost Burden of COPD in the United States From 2016 to 2019 and Projections Through 2029,” Chest 165 (2024): 1093–1106.

3. Aaron S. D., Vandemheen K. L., Whitmore G. A., et al., “Early Diagnosis and Treatment of COPD and Asthma—A Randomized, Controlled Trial,” New England Journal of Medicine 390, no. 22 (2024): 2061–2073, 10.1056/NEJMoa2401389.

4. Chen Q., Fan Y., Huang K., et al., “Cost-Effectiveness of Population-Based Screening for Chronic Obstructive Pulmonary Disease in China: A Simulation Modeling Study,” Lancet Regional Health – Western Pacific 46 (2024): 101065.

5. Leung C. C., “Use of Spirometry to Detect Airflow Obstruction,” Respirology 29 (2024): 443–444

6. Zhang Y., Gai X., Chu H., Qu J., Li L., and Sun Y., “Prevalence of Non-Smoking Chronic Obstructive Pulmonary Disease and Its Risk Factors in China: A Systematic Review and Meta-Analysis,” BMC Public Health 24 (2024): 3010.

7. Pandey A. K., Verma A. K., Singh A., et al., “The Severity of Non-Smoking Chronic Obstructive Pulmonary Disease Is Correlated With Biomass Fuel Exposure and COPD Assessment Test Score,” Lung India 41 (2024): 251–258.

8. Rentschler J. and Leonova N., “Global Air Pollution Exposure and Poverty,” Nature Communications 14 (2023): 4432.

9. Ma S., Cheng D., Tang Y., et al., “Investigation of Oxidative Potential of Fresh and O(3)-aging PM(2.5) From Various Emission Sources Across Urban and Rural Regions,” Journal of Environmental Sciences 151 (2025): 608–615.

10. Chen J., Braun D., Christidis T., et al., “Long-Term Exposure to Low-Level PM2.5 and Mortality: Investigation of Heterogeneity by Harmonizing Analyses in Large Cohort Studies in Canada, United States, and Europe,” Environmental Health Perspectives 131 (2023): 127003.

11. Wei T., Chen C., Yang Y., et al., “Associations Between Short-Term Exposure to Ambient Air Pollution and Lung Function in Adults,” Journal of Exposure Science & Environmental Epidemiology 34 (2024): 886–894.

12. Lee H. W., Lee H. J., Oh S., Lee J. K., Heo E. Y., and Kim D. K., “Combined Effect of Changes in NO(2), O(3), PM(2.5), SO(2) and CO Concentrations on Small Airway Dysfunction,” Respirology 29 (2024): 379–386.

13. Yang I. A., Jenkins C. R., and Salvi S. S., “Chronic Obstructive Pulmonary Disease in Never-Smokers: Risk Factors, Pathogenesis, and Implications for Prevention and Treatment,” Lancet Respiratory Medicine 10 (2022): 497–511.

14. Vaughan A., Stevanovic S., Jafari M., et al., “Primary Human Bronchial Epithelial Cell Responses to Diesel and Biodiesel Emissions at an Air-Liquid Interface,” Toxicology In Vitro 57 (2019): 67–75.

15. Vaughan A., Stevanovic S., Jafari M., et al., “The Effect of Diesel Emission Exposure on Primary Human Bronchial Epithelial Cells From a COPD Cohort: N-Acetylcysteine as a Potential Protective Intervention,” Environmental Research 170 (2019): 194–202.

16. Guo X., Yang S., Zhu H., et al., “Involvement of M2 Macrophages Polarization in PM2.5-Induced COPD by Upregulating MMP12 via IL4/STAT6 Pathway,” Ecotoxicology and Environmental Safety 283 (2024): 116793.

17. Cheng P. P., Yu F., Chen S. J., et al., “PM2.5 Exposure-Induced Senescence-Associated Secretory Phenotype in Airway Smooth Muscle Cells Contributes to Airway Remodeling,” Environmental Pollution 347 (2024): 123674.

18. Li S., Qu L., Zhou L., et al., “Biomass Fuels Related-PM(2.5) Promotes Lung Fibroblast-Myofibroblast Transition Through PI3K/AKT/TRPC1 Pathway,” Ecotoxicology and Environmental Safety 276 (2024): 116309.

19. Niu Y., Zhang L., Guo S., and Wu S., "In Vivo and In Vitro Models of PM2.5 Induced COPD: Focus on the Role of RTA-408," International Journal of Chronic Obstructive Pulmonary Disease 19 (2024): 2239–2257.
20. Barnes P. J., "Inflammatory Endotypes in COPD," Allergy 74 (2019): 1249–1256.
21. Fraughen D. D., Ghosh A. J., Hobbs B. D., et al., "Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency Improves Survival and Is Decoupled From Spirometric Decline-A Multinational Registry Analysis," American Journal of Respiratory and Critical Care Medicine 208 (2023): 964–974.
22. Liu G., Tiotiu A., and Hansbro P. M., "Mast Cell Chymase-1 and Tryptases: Therapeutic Targets for COPD?," Expert Opinion on Therapeutic Targets 29 (2025): 9–12
23. Barnes P. J., "Inflammatory Mechanisms in Patients With Chronic Obstructive Pulmonary Disease," Journal of Allergy and Clinical Immunology 138 (2016): 16–27.
24. Appleton L. K., Hanania N. A., and Adrish M., "Personalized COPD Care: The Future of Precision-Based Therapies," Journal of Clinical Medicine 13, no. 21 (2024): 6339, 10.3390/jcm13216339.
25. Bafadhel M., Peterson S., De Blas M. A., et al., "Predictors of Exacerbation Risk and Response to Budesonide in Patients With Chronic Obstructive Pulmonary Disease: A Post-Hoc Analysis of Three Randomised Trials," Lancet Respiratory Medicine 6 (2018): 117–126.
26. Cabrera López C., Sánchez Santos A., Lemes Castellano A., et al., "Eosinophil Subtypes in Adults With Asthma and Adults With Chronic Obstructive Pulmonary Disease," American Journal of Respiratory and Critical Care Medicine 208 (2023): 155–162.
27. Sunata K., Miyata J., Kawashima Y., et al., "Inflammatory Profile of Eosinophils in Asthma-COPD Overlap and Eosinophilic COPD: A Multi-Omics Study," Frontiers in Immunology 15 (2024): 1445769.
28. Leung C., Park H. Y., Li X., et al., "Transcriptomic Profiling of the Airway Epithelium in COPD Links Airway Eosinophilia to Type 2 Inflammation and Corticosteroid Response," European Respiratory Journal 65 (2025): 2401875.
29. Hobbs B. D., Morrow J. D., Wang X. W., et al., "Identifying Chronic Obstructive Pulmonary Disease From Integrative Omics and Clustering in Lung Tissue," BMC Pulmonary Medicine 23, no. 1 (2023): 115, 10.1186/s12890-023-02389-5.
30. Moll M. and McDonough J., "Piece of Cake: Slicing Through the Complex Layers of Chronic Obstructive Pulmonary Disease With Lung Tissue Network Analysis," American Journal of Respiratory and Critical Care Medicine 210 (2024): 1174–1176.
31. Olvera N., Sánchez-Valle J., Núñez-Carpintero I., et al., "Lung Tissue Multilayer Network Analysis Uncovers the Molecular Heterogeneity of Chronic Obstructive Pulmonary Disease," American Journal of Respiratory and Critical Care Medicine 210 (2024): 1219–1229.
32. Stanojevic S., Kaminsky D. A., Miller M. R., et al., "ERS/ATS Technical Standard on Interpretive Strategies for Routine Lung Function Tests," European Respiratory Journal 60 (2022): 2101499.
33. Cadham C. J., Oh H., Han M. K., et al., "The Prevalence and Mortality Risks of PRISm and COPD in the United States From NHANES 2007-2012," Respiratory Research 25, no. 1 (2024): 208, 10.1186/s12931-024-02841-y.
34. Tan D. J., Lodge C. J., Walters E. H., et al., "Can we Use Lung Function Thresholds and Respiratory Symptoms to Identify Pre-Chronic Obstructive Pulmonary Disease? A Prospective, Population-Based Cohort Study," American Journal of Respiratory and Critical Care Medicine 209 (2024): 1431–1440
35. Lam A. H. S., Alhajri S. A., Potts J., et al., "Optimal Spirometry Thresholds for the Prediction of Chronic Airflow Obstruction: A Multinational Longitudinal Study," ERJ Open Research 11 (2025): 00624–2024.
36. Kogo M., Sato S., Muro S., et al., "Longitudinal Changes and Association of Respiratory Symptoms With Preserved Ratio Impaired Spirometry (PRISm): The Nagahama Study," Annals of the American Thoracic Society 20 (2023): 1578–1586.
37. Petrie K., Abramson M. J., and George J., "Smoking, Respiratory Symptoms, Lung Function and Life Expectancy: A Longitudinal Study of Ageing," Respirology 29 (2024): 471–478.
38. Ritchie A. I., Donaldson G. C., Hoffman E. A., et al., "Structural Predictors of Lung Function Decline in Young Smokers With Normal Spirometry," American Journal of Respiratory and Critical Care Medicine 209 (2024): 1208–1218.
39. Chaudhary M. F. A., Awan H. A., Gerard S. E., et al., "Deep Learning Estimation of Small Airways Disease From Inspiratory Chest CT: Clinical Validation, Repeatability, and Associations With Adverse Clinical Outcomes in COPD," American Journal of Respiratory and Critical Care Medicine (2025), 10.1164/rccm.202409-1847OC.
40. Dunican E. M., Elicker B. M., Gierada D. S., et al., "Mucus Plugs in Patients With Asthma Linked to Eosinophilia and Airflow Obstruction," Journal of Clinical Investigation 128 (2018): 997–1009.
41. Flynn C. and Brightling C., "Picture This: The Future of Imaging Biomarkers in COPD," Respirology 29 (2024): 932–934.
42. Dunican E. M., Elicker B. M., Henry T., et al., "Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers," American Journal of Respiratory and Critical Care Medicine 203 (2021): 957–968.

43. Mettler S. K., Nath H. P., Grumley S., et al., "Silent Airway Mucus Plugs in COPD and Clinical Implications," Chest 166 (2024): 1010–1019.
44. Tanabe N., Shimizu K., Shima H., et al., "Computed Tomography Mucus Plugs and Airway Tree Structure in Patients With Chronic Obstructive Pulmonary Disease: Associations With Airflow Limitation, Health-Related Independence and Mortality," Respirology 29 (2024): 951–961.
45. Wan E., Yen A., Elalami R., et al., "Airway Mucus Plugs on Chest Computed Tomography Are Associated With Exacerbations in COPD," American Journal of Respiratory and Critical Care Medicine 211 (2025): 814–822, 10.1164/rccm.202403-0632OC.
46. Li X., Feng S., Yang Y., et al., "Association Between Airway Mucus Plugs and Risk of Moderate-To-Severe Exacerbations in COPD Patients:Results From a Chinese Prospective Cohort Study," Chest (2025), 10.1016/j.chest.2025.03.026
47. Serajeddini H., Eddy R. L., Licskai C., McCormack D. G., and Parraga G., "FEV(1) and MRI Ventilation Defect Reversibility in Asthma and COPD," European Respiratory Journal 55 (2020): 1901947, 10.1183/13993003.01947-2019.
48. Elbehairy A. F., Marshall H., Naish J. H., et al., "Advances in COPD Imaging Using CT and MRI: Linkage With Lung Physiology and Clinical Outcomes," European Respiratory Journal 63 (2024): 2301010.
49. Wang Z., Bier E. A., Swaminathan A., et al., "Diverse Cardiopulmonary Diseases Are Associated With Distinct Xenon Magnetic Resonance Imaging Signatures," European Respiratory Journal 54 (2019): 1900831.
50. Meldrum O. W., Donaldson G. C., Narayana J. K., et al., "Accelerated Lung Function Decline and Mucus-Microbe Evolution in Chronic Obstructive Pulmonary Disease," American Journal of Respiratory and Critical Care Medicine 210, no. 3 (2024): 298–310, 10.1164/rccm.202306-1060OC.
51. van Rossem I., Hanon S., Verbanck S., and Vanderhelst E., "Blood Eosinophil Counts in Chronic Obstructive Pulmonary Disease: Adding Within-Day Variability to the Equation," American Journal of Respiratory and Critical Care Medicine 205 (2022): 727–729.
52. Van Rossem I., Hanon S., Vansintejan J., Verbanck S., and Vanderhelst E., "Is Fractional Exhaled Nitric Oxide Ready to Be a Biomarker? Within-Day Variability in Stable COPD," Respirology 29, no. 9 (2024): 835–837, 10.1111/resp.14786.
53. Bhatt S. P., Rabe K. F., Hanania N. A., et al., "Dupilumab for COPD With Type 2 Inflammation Indicated by Eosinophil Counts," New England Journal of Medicine 389 (2023): 205–214.
54. Bhatt S. P., Rabe K. F., Hanania N. A., et al., "Dupilumab for COPD With Blood Eosinophil Evidence of Type 2 Inflammation," New England Journal of Medicine 390 (2024): 2274–2283.
55. McDonald V. M. and Gibson P. G., "Treatable Traits-Where We Are, Where We Are Headed," Respirology 29 (2024): 539–541.
56. McDonald V. M. and Holland A. E., "Treatable Traits Models of Care," Respirology 29 (2024): 24–35.
57. Srikanthan K., Kistemaker L., Slebos D.-J., et al., "Targeted Lung Denervation Modulates the Mucosal Epithelial Transcriptome in COPD," ERJ Open Research 8, no. 4 (2022): 00146–02022, 10.1183/23120541.00146-2022
58. Hartman J. E., Herth F. J. F., Shah P., et al., "Computed Tomographic Airway Morphology After Targeted Lung Denervation Treatment in COPD," Respiratory Medicine 206 (2023): 107059, 10.1016/j.rmed.2022.107059.
59. Dharmage S. C., Faner R., and Agustí A., "Treatable Traits in Pre-COPD: Time to Extend the Treatable Traits Paradigm Beyond Established Disease," Respirology 29 (2024): 551–562.
60. Pavord I. D., Chanez P., Criner G. J., et al., "Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease," New England Journal of Medicine 377 (2017): 1613–1629.
61. Criner G. J., Celli B. R., Brightling C. E., et al., "Benralizumab for the Prevention of COPD Exacerbations," New England Journal of Medicine 381 (2019): 1023–1034.
62. Haldar K., Mistry V., Richardson M., et al., "Effect of Benralizumab Treatment on the Airway Microbiome in COPD," ERJ Open Research 11, no. 2 (2025): 00802-2024, 10.1183/23120541.00802-2024.
63. Ramakrishnan S., Russell R. E. K., Mahmood H. R., et al., "Treating Eosinophilic Exacerbations of Asthma and COPD With Benralizumab (ABRA): A Double-Blind, Double-Dummy, Active Placebo-Controlled Randomised Trial," Lancet Respiratory Medicine 13 (2025): 59–68.
64. Bhatt S. P., Rabe K. F., Hanania N. A., et al., "Dupilumab for Chronic Obstructive Pulmonary Disease With Type 2 Inflammation: A Pooled Analysis of Two Phase 3, Randomised, Double-Blind, Placebo-Controlled Trials," Lancet Respiratory Medicine 13 (2025): 234–243.
65. Singh D., Brightling C. E., Rabe K. F., et al., "Efficacy and Safety of Tezepelumab Versus Placebo in Adults With Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COURSE): A Randomised, Placebo-Controlled, Phase 2a Trial," Lancet Respiratory Medicine 13, no. 1 (2025): 47–58, 10.1016/S2213-2600(24)00324-2.
66. Rabe K. F., Celli B. R., Wechsler M. E., et al., "Safety and Efficacy of Itepekimab in Patients With Moderate-To-Severe COPD: A Genetic Association Study and Randomised, Double-Blind, Phase 2a Trial," Lancet Respiratory Medicine 9 (2021): 1288–1298.

67. Yousuf A. J., Mohammed S., Carr L., et al., "Astegolimab, an Anti-ST2, in Chronic Obstructive Pulmonary Disease (COPD-ST2OP): A Phase 2a, Placebo-Controlled Trial," Lancet Respiratory Medicine 10 (2022): 469–477.
68. Singh D., Guller P., Reid F., et al., "A Phase 2a Trial of the IL-33 mAb Tozorakimab in Patients With COPD: FRONTIER-4," European Respiratory Journal (2025): 2402231, 10.1183/13993003.02231-2024.
69. Wang Z., Qiu Y., Ji X., and Dong L., "Effects of Smoking Cessation on Individuals With COPD: A Systematic Review and Meta-Analysis," Frontiers in Public Health 12 (2024): 1433269.
70. Siegel S. D., Lerman C., Flitter A., and Schnoll R. A., "The Use of the Nicotine Metabolite Ratio as a Biomarker to Personalize Smoking Cessation Treatment: Current Evidence and Future Directions," Cancer Prevention Research 13 (2020): 261–272.
71. Qin R., Liu Z., Cheng A.-q., et al., "Efficacy of Varenicline or Bupropion and Its Association With Nicotine Metabolite Ratio Among Smokers With COPD," Respirology 29, no. 6 (2024): 479–488, 10.1111/resp.14702.
72. Cinciripini P. M., Green C. E., Shete S., et al., "Smoking Cessation After Initial Treatment Failure With Varenicline or Nicotine Replacement: A Randomized Clinical Trial," Journal of the American Medical Association 331 (2024): 1722–1731.
73. Rungruanghiranya S., Tulatamakit S., Chittawatanarat K., et al., "Efficacy and Safety of Cytisine Versus Nortriptyline for Smoking Cessation: A Multicentre, Randomized, Double-Blinded and Placebo-Controlled Trial," Respirology 29 (2024): 880–887.
74. Livingstone-Banks J., Fanshawe T. R., Thomas K. H., et al., "Nicotine Receptor Partial Agonists for Smoking Cessation," Cochrane Database of Systematic Reviews 5, no. 5 (2023): Cd006103, 10.1002/14651858.CD006103.pub8.
75. Puljević C., Stjepanović D., Meciar I., et al., "Systematic Review and Meta-Analyses of Cytisine to Support Tobacco Cessation," Addiction 119 (2024): 1713–1725.
76. Auer R., Schoeni A., Humair J. P., et al., "Electronic Nicotine-Delivery Systems for Smoking Cessation," New England Journal of Medicine 390 (2024): 601–610.
77. Allbright K., Villandre J., Crotty Alexander L. E., et al., "The Paradox of the Safer Cigarette: Understanding the Pulmonary Effects of Electronic Cigarettes," European Respiratory Journal 63 (2024): 2301494
78. Caponnetto P., Campagna D., Ahluwalia J. S., et al., "Varenicline and Counseling for Vaping Cessation: A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Trial," BMC Medicine 21 (2023): 220.
79. Caponnetto P., Spicuzza L., Campagna D., et al., "Varenicline for Smoking Cessation in Individuals Who Smoke Cigarettes and Use Electronic Cigarettes: A Double-Blind, Randomised, Placebo-Controlled Phase 3 Trial," EClinicalMedicine 66 (2023): 102316.
80. Ran B., Zhang Y., Wu Y., and Wen F., "Association Between Depression and COPD: Results From the NHANES 2013-2018 and a Bidirectional Mendelian Randomization Analysis," Expert Review of Respiratory Medicine 17 (2023): 1061–1068.
81. Sharma P., Scheffer K., Louis M., Aitken C. R., Adams L., and Morris N. R., "Effect of Experimental Modulation of Mood on Exertional Dyspnoea in Chronic Obstructive Pulmonary Disease," Respirology 29 (2024): 201–208.
82. Pascoe A. and Smallwood N., "Breaking the Spiral: How Negative Mood Can Fuel Exertional Breathlessness in People With Chronic Obstructive Pulmonary Disease," Respirology 29 (2024): 193–194.
83. Higginson I. J., Brown S. T., Oluyase A. O., et al., "Mirtazapine to Alleviate Severe Breathlessness in Patients With COPD or Interstitial Lung Diseases (BETTER-B): An International, Multicentre, Double-Blind, Randomised, Placebo-Controlled, Phase 3 Mixed-Method Trial," Lancet Respiratory Medicine 12 (2024): 763–774.
84. Meneses-Echavez J. F., Chavez Guapo N., Loaiza-Betancur A. F., Machado A., and Bidonde J., "Pulmonary Rehabilitation for Acute Exacerbations of COPD: A Systematic Review," Respiratory Medicine 219 (2023): 107425.
85. Muñoz Montiel A., Ruiz-Esteban P., Del Doménech Río A., Valdivielso P., Sánchez Chaparro M., and Olveira C., "The Effect of Pulmonary Rehabilitation on Cardiovascular Risk, Oxidative Stress and Systemic Inflammation in Patients With COPD," Respiratory Medicine 232 (2024): 107740.
86. van der Molen M. C., Posthuma R., Hartman J. E., et al., "Impact and Timing of Pulmonary Rehabilitation in Patients Undergoing Bronchoscopic Lung Volume Reduction With Endobronchial Valves: A Multicentre Randomized Controlled Trial in Patients With Severe Emphysema," Respirology 29 (2024): 694–703.
87. Strange C. and Talley M., "Winning the Tour de France With Endobronchial Valve Therapy Without Pulmonary Rehabilitation," Respirology 29 (2024): 651–652.
88. Cranston J. M., Crockett A. J., Moss J. R., and Alpers J. H., "Domiciliary Oxygen for Chronic Obstructive Pulmonary Disease," Cochrane Database of Systematic Reviews 2005 (2005): Cd001744.
89. García-Talavera I., Figueira-Gonçalves J. M., Esteban C., et al., "Oxygen Therapy Could Improve Survival in Patients With Early Desaturation in the 6-Minute Walk Test: A Post Hoc Analysis," Respirology 29 (2024): 340–343.
90. Cobb K., Kenyon J., Lu J., et al., "COPD Is Associated With Increased Cardiovascular Disease

Risk Independent of Phenotype," Respirology 29 (2024): 1047–1057.
91. Cochrane B., "COPD: The Forgotten Cardiovascular Risk," Respirology 29 (2024): 1013–1014.
92. Marin J. M., Soriano J. B., Marin-Oto M., et al., "Sleep-Disordered Breathing in Patients With COPD: Prevalence and Outcomes," Annals of the American Thoracic Society (2025), 10.1513/AnnalsATS.202501-030OC
93. Zhang X., Gray A. R., and Hancox R. J., "Predictors of Lung Function in Early Adulthood: A Population-Based Cohort Study," Respirology 29 (2024): 897–904.
94. Garcia-Aymerich J. and Peralta G. P., "Childhood Physical Inactivity and Excess Weight: Two Potentially Modifiable Risk Factors for COPD," Respirology 29 (2024): 856–857.
95. Ruane L. E., Denton E., Bardin P. G., and Leong P., "Dysfunctional Breathing or Breathing Pattern Disorder: New Perspectives on a Common but Clandestine Cause of Breathlessness," Respirology 29 (2024): 863–866.
96. van Dixhoorn J. and Duivenvoorden H. J., "Efficacy of Nijmegen Questionnaire in Recognition of the Hyperventilation Syndrome," Journal of Psychosomatic Research 29 (1985): 199–206.
97. Law N., Ruane L. E., Low K., Hamza K., and Bardin P. G., "Dysfunctional Breathing Is More Frequent in Chronic Obstructive Pulmonary Disease Than in Asthma and in Health," Respiratory Physiology & Neurobiology 247 (2018): 20–23