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Contemporary Concise Review 2024: Chronic Obstructive Pulmonary Disease

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SUMMARY OF KEY POINTS

- Non-smoking COPD is common in LMICs, especially in women. Biomass fuel and air pollution are major risk factors with distinct pathophysiology.
- The 'eosinophilic' endotype in COPD is biologically distinct from asthma.
- PRISm, FEV_1/FVC Z-scores, and quantitative CT improve early COPD detection.
- Dupilumab (anti-IL-4/IL-13) improved exacerbations and lung function in COPD with blood eosinophils ≥300 cells/μL. Mechanisms are currently being investigated.
- Smoking cessation remains pivotal. Nicotine metabolite ratio (NMR) can guide pharmacotherapy. Cytisine and varenicline are effective; e-cigarettes pose safety concerns.
- Mood disorders and dysfunctional breathing are common in COPD. Addressing these can reduce symptom burden and improve quality of life.
- Comorbidity management, particularly of cardiovascular risk, obesity, and sleep-disordered breathing, is integral to holistic COPD care.

1 | Introduction

Chronic obstructive lung disease (COPD) is a common airway disease which is a major cause of morbidity and mortality globally. Over the past three decades, COPD ranked as the third leading cause of death worldwide, until dropping to fourth place in 2021 due to the emergence of COVID-19. The mortality rates are higher in South Asia, Southeast Asia, East Asia, and Oceania [1]. In addition to health-related issues, COPD entails substantial healthcare expenditures and indirect costs due to lost productivity and disability. A study from the United States (US) showed that the annual medical expenditure of COPD patients was approximately 2.5 times higher than that of the patients without COPD. The COPD-specific attributable cost was $25.3 billion US dollars (USD) in 2019 (or $1445 USD per patient), with projections rising to $60.5 billion USD by 2029 [2]. Notably, these estimates do not include indirect costs such as loss of productivity and disability affecting both patients and caregivers. Timely

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diagnosis and providing personalised, comprehensive treatment yield clinical outcome improvement [3]. Screening policies either based on questionnaires alone or combined with spirometry seem to be cost-effective [4].

This review aims to summarise key evidence-based findings from the previous year with a focus on the patho-physiobiology of COPD, investigation tools, and multimodal treatment options encompassing both pharmacological and non-pharmacological therapies, as well as the management of comorbidities.

2 | Non-Smoking COPD

Summary

- In LMICs, 30%–40% of COPD cases are unrelated to smoking, particularly among women with biomass fuel exposure and air pollution identified as key contributing factors.
- PM2.5 exposure contributes to mortality and small airway dysfunction.
- Distinct inflammatory and remodelling mechanisms in non-smoking COPD suggest opportunities for targeted intervention.

Tobacco smoking is a well-established primary cause of COPD. However, in low- and middle-income countries (LMICs), it accounts for only 30%–40% of COPD cases [5]. A recent systematic review and meta-analysis from China, involving nearly 500,000 participants, found that 41.1% of COPD patients were never-smokers, with a markedly higher proportion among women (81.3%) compared to men (22.3%). The study also demonstrated a significant association between biomass fuel and COPD in never-smokers (OR: 1.25; 95% CI: 1.06–1.44) [6]. Similarly, a study from India reported a higher prevalence of non-smoking COPD among women, identifying biomass fuel exposure as a major risk factor [7].

Indoor and outdoor air pollution are increasingly recognised for their health complications globally. Approximately 7.3 billion people, with 80% in LMICS, are directly exposed to unsafe average annual particulate matter$_{2.5}$ ($PM_{2.5}$) levels [8]. $PM_{2.5}$, an ultrafine particle capable of penetrating deep into small airways and alveoli due to its size, exerts toxic effects from various chemical compositions and oxidative activity [9]. Long-term exposure to $PM_{2.5}$, despite a low level, has been associated with increased all-cause mortality. A pooled analysis from large cohort studies from Canada (MAPLE), the US (Medicare), and Europe (Elapse) approximates a hazard ratio of 1.04 for all-cause mortality per 5 $\mu g/m^3$ increase in $PM_{2.5}$ concentration [10].

Small airway function is significantly impacted by inhaled pollutants. Forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%-75\%}$) has widely been used to evaluate small airway dysfunction due to its simplicity and accessibility from spirometry data, despite its lack of reproducibility and forced vital capacity (FVC) dependence. More data are emerging with respiratory oscillometry measurements. Increased air pollution exposure, including $PM_{2.5}$, PM_{10}, Nitrogen dioxide (NO_2), Sulphur dioxide (SO_2), and Carbon monoxide (CO), has been related to a $FEF_{25\%-75\%}$ decrease with confirmed effects across various populations [11, 12]. Furthermore, there was a significant correlation between the annual change in air pollution concentration and small airway disease [12].

Although the exact underlying mechanism is still elusive, several pathways have been studied (Figure 1) [13–15]. One mechanistic study in animal models demonstrated that $PM_{2.5}$ exposure can activate the interleukin (IL)-4/Signal transducer and activator of transcription (STAT)6 pathway, promoting M2 macrophage polarisation and matrix metalloproteinase (MMP)-12 upregulation, ultimately resulting in alveolar epithelial barrier dysfunction and excessive extracellular matrix (ECM) degradation [16]. $PM_{2.5}$ has been shown to induce airway remodelling through up-regulation of collagen-I and alpha-smooth muscle actin (α-SMA) expression, involving the airway smooth muscle cells senescence through autophagy-induced GATA Binding Protein 4 (GATA4)/Tumour necrosis factor receptor associated factor 6 (TRAF6)/nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) signalling [17]. A separate study, focusing on biomass fuels-related $PM_{2.5}$, demonstrated fibroblast-to-myofibroblast transition, with the possibility of mediation by phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT)/Transient receptor potential cation channel, subfamily C, member 1 (TRPC1) [18]. Another pathway identified is related to the nuclear factor NF-E2-associated factor (Nrf2) pathway, which plays a role in modulating anti-inflammatory and antioxidant stress response in the lung [19]. These emerging mechanistic insights highlight the distinct biological pathways underlying COPD development from various non-smoking exposures, which may differ from those in smoking-related COPD, and offer promise for novel therapeutic strategies aimed at preventing disease progression rather than merely alleviating symptoms.

3 | Airway Inflammation and COPD Endotypes

Summary

- COPD airway inflammation involves diverse immune and structural cell interactions.
- 'Eosinophilic COPD' may represent a distinct entity from 'eosinophilic asthma,' with differing biology and treatment responses.
- Multi-omics and machine learning are helping define COPD endotypes with potential for precision treatment.

COPD is a chronic inflammatory condition with two key pathological sites in the respiratory system: peribronchovascular

fibrosis in the small airways and emphysematous changes caused by alveolar wall destruction. Clinical phenotypes of COPD patients are varied, ranging from different aetiologies (smoking versus non-smoking) and clinical presentations (breathlessness versus chronic productive cough or frequent exacerbator versus non-exacerbator). While a clinical-based approach can categorise patients into distinct groups, it has limited utility in guiding treatment aimed at halting further lung damage. Two identified genetic conditions predisposing to COPD development are Alpha-1 antitrypsin deficiency (AATD) and telomere polymorphisms [20]. Identifying AATD and providing augmentation therapy has shown survival benefits [21].

The COPD airway inflammatory pathway not only involves neutrophils, macrophages, and eosinophils, but also a diverse array of cells in the immune system: CD4+ T cells, CD8+ T cells, monocytes, mast cells, and innate lymphoid cells (ILC) [22]. In addition, structural cells (airway epithelial cells, endothelial cells, and fibroblasts) contribute to the inflammatory process through complex cytokine pathways (Figure 1) [20, 23, 24].

Blood eosinophils have been widely used as a biomarker for COPD management as a predictor of acute exacerbation and response to inhaled corticosteroid treatment (ICS) [25]. The concept of 'Eosinophilic COPD' has garnered increasing interest, largely due to the success of eosinophil-targeted biologic therapies in asthma. However, recent evidence suggests that not all eosinophils are functionally equivalent. A study comparing eosinophil subtypes from stable asthma and COPD patients revealed a differing proportion of inflammatory eosinophils (iEos), which were more abundant in patients with asthma, regardless of total eosinophil count. iEos also express more IL-5 receptors than resident eosinophils. Interestingly, iEos number in COPD patients was not associated with inhaled corticosteroid use, disease severity, or exacerbation rate [26]. These findings raise important questions about whether eosinophils function as bystander biomarkers in COPD and challenge the reliability of blood eosinophil counts as a standalone marker for guiding personalised treatment (discussed further under section 6.1 on biologics).

Advances in multi-omics technologies have enhanced our understanding of COPD at the molecular level. Proteomics, transcriptomics, and lipidomics profiles of eosinophils isolated from COPD and Asthma-COPD overlap (ACO) patients demonstrated the role of IL-33, TNF-α, and IFN-γ in eosinophil activation pathways [27]. Transcriptomic analysis using gene expression from airway epithelial cells in COPD with airway eosinophilia (defined by bronchoalveolar lavage fluid eosinophils > 1%) demonstrates increasing expression of Type 2 airway inflammation, IL-13, and mast cell activation. Treatment with inhaled corticosteroid ICS leads to a reduction of this signature [28]. Furthermore, data from multi-omics analysis also confirmed the divergence of COPD pathobiology. Similar clinical phenotypes can be driven by molecularly distinct small airways and immune response patterns. Integrating each omics data algorithm with machine learning also provided promising results to identify lung-specific COPD endotypes [29–31].

4 | Investigations in COPD

Summary

- Spirometry remains essential but may miss early or atypical disease.
- Applying PRISm and FEV_1/FVC Z-score criteria enhances early identification of individuals at risk for developing COPD.
- Quantitative CT imaging allows early detection of small airway disease and mucus pathology.
- Functional MRI offers radiation-free structural and functional assessment of the lungs, though its clinical use is limited by availability.

Diagnosis of COPD comprises the presence of respiratory symptoms and relevant risk factors, followed by diagnosis confirmation with spirometry demonstrating post-bronchodilator forced expiratory volume in 1 s (FEV_1)/FVC ratio less than 0.7. However, recent guidelines recommend using the lower limit of normal of this ratio as a diagnostic cut-off for airflow limitation, as it physiologically declines with age [32]. Using a fixed ratio strategy may lead to underdiagnosis of COPD in young individuals. The term Preserved Ratio Impaired Spirometry (PRISm) was mentioned recently, defined as an FEV_1/FVC ≥ 0.7 with abnormal spirometry (i.e., $FEV_1 < 80\%$). Analysis of the US National Health and Nutritional Examination Survey (2007–2012), using pre- not post-bronchodilator (BD), estimated PRISm prevalence at 9.6%–10.2% compared to 13.1%–14.3% of COPD, with higher rates observed in females [33]. The Tasmanian Longitudinal Health Study further evaluated spirometry interpretation using a cut-off of pre-BD FEV_1/FVC Z-score at the 10th percentile, with participants followed from age 45 to 53. This cohort study found that individuals meeting this criterion had a 36-fold increased risk of developing COPD over 8 years, with a sensitivity of 88% and specificity of 87% [34]. The BOLD cohort study ($n = 30{,}757$; median follow-up of 8.4 years) demonstrated that applying a pre-bronchodilator (pre-BD) FEV_1/FVC Z-score threshold at the 9th percentile facilitates the early detection of airflow obstruction, particularly among current smokers [35]. The Nagahama study from Japan reported that 53% of individuals with PRISm initially presented with respiratory symptoms, particularly dyspnoea, while 39% of asymptomatic participants developed symptoms within 5 years. PRISm was identified as an independent risk factor for developing COPD regardless of smoking history or comorbidities [36].

Beyond its diagnostic role, spirometry also provides the mortality prognosis. In the ex-smoker and current smoker populations, using an FEV_1/FVC cut-off of 0.7 provided benefits in survival outcomes. The study in older adults using a remaining life expectancy (LE) as a surrogate for future mortality risk revealed the lower remaining LE in the ex-smoker and non-smoker group with respiratory symptoms with FEV_1/FVC < 0.7 compared to the group with FEV_1/FVC $\geq 0/7$ [37].

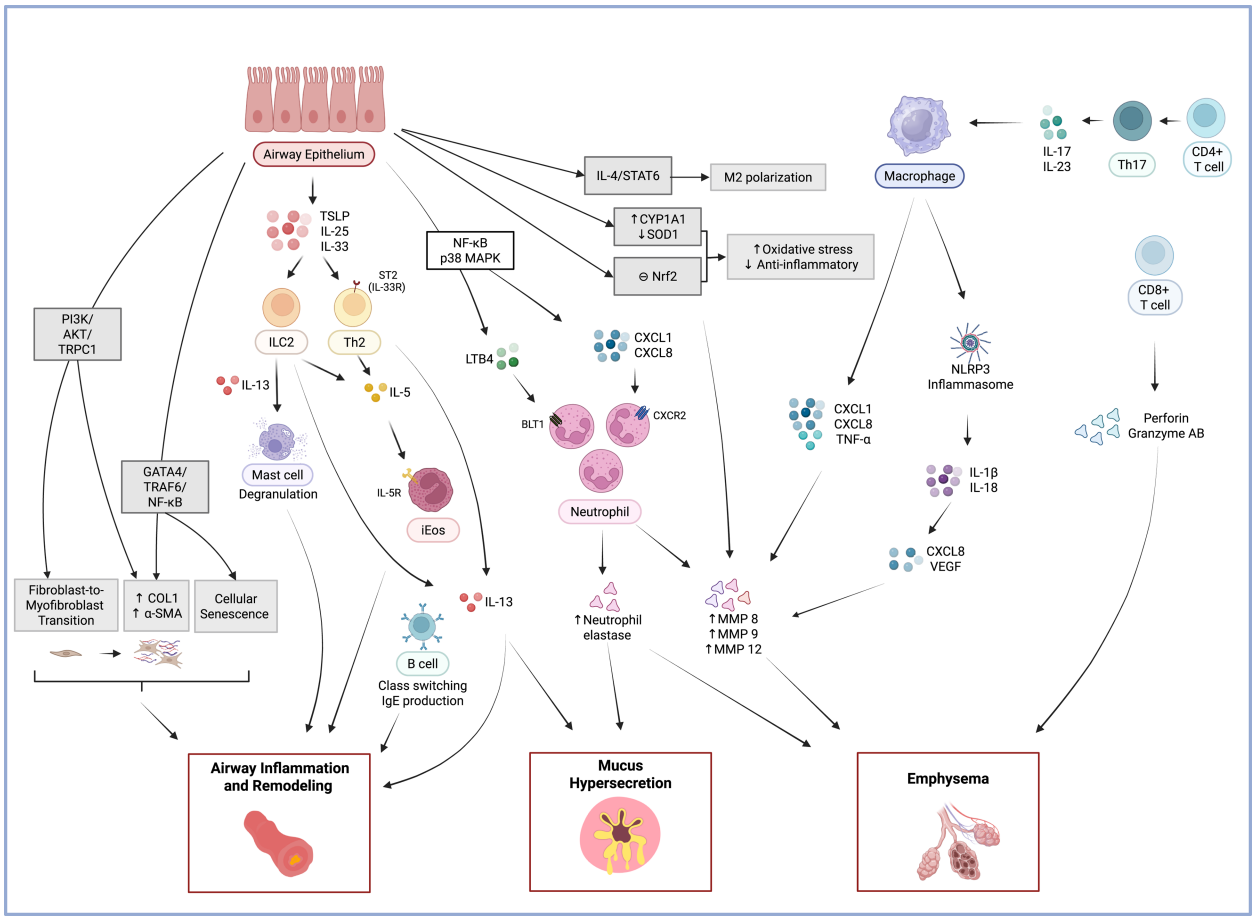

FIGURE 1 | Integrated Inflammatory Pathways in COPD Pathophysiology. Tobacco smoking and air pollution exert effects on the airway epithelium and multiple immune cell populations. The resulting complex interactions of gene expression and cytokine signalling drive airway inflammation and remodelling, mucus hypersecretion, and alveolar destruction leading to emphysema. Mechanistic pathways specific to non-smoking-related COPD are highlighted within the grey boxes. This original figure was created by the authors using BioRender.com. α-SMA, alpha smooth muscle actin; AKT, protein kinase B; BLT1, leukotriene B4 receptor 1; COL1, collagen type I; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; CYP, cytochrome P450; GATA4, GATA binding protein 4; iEos, inflammatory eosinophils; IgE, immunoglobulin E; IL, interleukin; IL-5R, interleukin-5 Receptor; ILC2, group 2 innate lymphoid cells; LTB4, leukotriene B4; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid 2–related Factor 2; PI3K, phosphoinositide 3-kinase; SOD1, superoxide dismutase 1; STAT6, signal transducer and activator of transcription 6; TRAF6, TNF receptor associated factor 6; TRPC1, transient receptor potential canonical channel 1; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

While physiologic measurement, such as spirometry, has limitations and is often considered a late-detection tool, advanced imaging techniques, particularly quantitative thoracic computer tomography (CT) have demonstrated promising value in detecting early structural changes associated with COPD. The BEACON cohort study, which included young smokers with preserved lung function ($FEV_1 > 80\%$ predicted), with a median age of 39 years and a mean smoking history of 16 pack-years, demonstrated a higher prevalence of air trapping (indicating of functional small airway disease), emphysema, and abnormalities of lung parenchyma and pulmonary vasculature. These abnormalities were associated with an accelerated FEV_1 decline [38]. Integrating generative artificial intelligence (AI) enables a reliable assessment of small airway disease from a single inspiratory CT scan and shows a significant association with FEV_1 deterioration [39].

Furthermore, CT imaging is an informative tool for characterising the underlying causes of airflow limitation and defining prognosis. Not only identifying emphysema, CT can be used to assess airway pathology and mucus plugging with several quantitative parameters, including the mucus plug score (number of bronchopulmonary segments with completely occluded mucus plugs) [40], lower total airway count (TAC), and the percentage of the wall area of the central airway (WA%) [41]. Among smokers with COPD, only one-third of smokers who had a high mucus score were noted for their mucus symptoms [42]. Conversely, one-third of COPD patients who have no cough or sputum production demonstrated a mucus plug on CT. Older age, female sex, and Blac race are the risk factors for silent mucus plugging [43]. A high mucus plug score has been associated with increased dyspnoea, a higher risk of exacerbations, oxygen desaturation, lower FEV_1 (independent

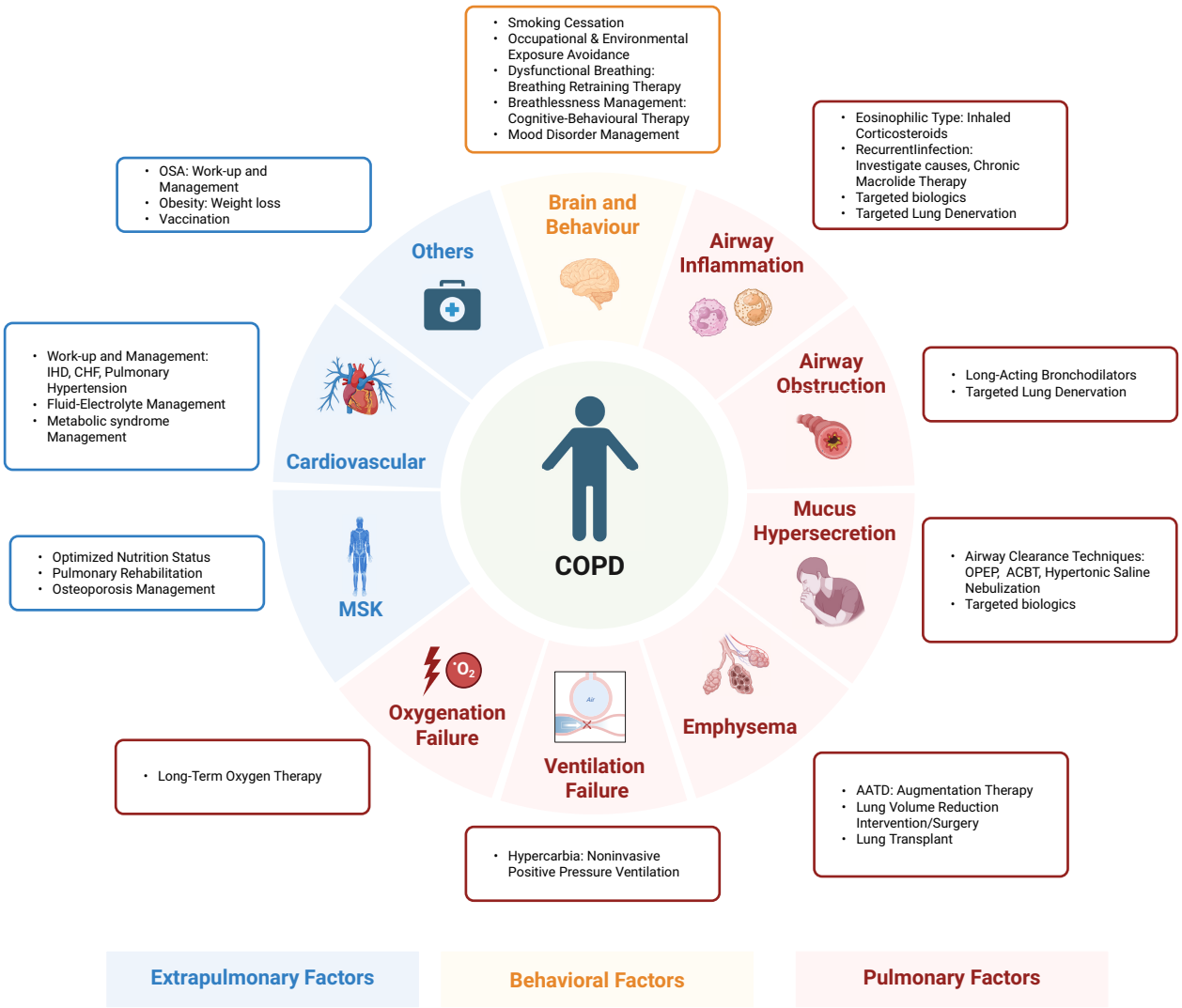

FIGURE 2 | Comprehensive COPD care. This original figure was created by the authors using BioRender.com. AATD, alpha-1 antitrypsin deficiency; ACBT, active cycle of breathing technique; CHF, congestive heart failure; IHD, ischemic heart disease; MSK, musculoskeletal; OPEP, oscillating positive expiratory pressure; OSA, obstructive sleep apnoea.

of emphysema), reduced total airway count (TAC), thicker airway walls, more extensive emphysema, and increased mortality [42–46].

Functional MRI is the imaging modality capable of assessing both structural (alveolar airspace size) and functional (ventilation and gas exchange) changes without radiation exposure. Ventilation defect percentage (VDP) measured using hyperpolarized ^{129}Xe MRI is a sensitive and effective method for small airway disease evaluation [47]. Apparent diffusion coefficient (ADC) and mean diffusive length scale (Lm_D) can be used to quantify alveolar airspace dimension [48]. Gas exchange efficiency can be evaluated through the dissolved-phase imaging of MRI [49]. These advanced imaging techniques not only offer new insights into the pathophysiology of COPD but also provide valuable tools for research and the evaluation of treatment outcomes. However, given their limited availability, their use in clinical practice should be targeted toward appropriately selected patients who are most likely to benefit. A summary of investigation tools for early COPD detection is provided in Table 1.

Mucus plugging contributes importantly to airflow obstruction in COPD and is considered one of COPD's treatable traits. Investigating airway-mucus milieu through multi-omic analysis holds a promise for categorising patients or novel therapeutic targets. A recent study of mucus properties–microbiome, using shotgun metagenomics and mucus biochemical and biophysical analysis, demonstrated a higher concentration of mucins (MUC5AC and MUC5B) as well as the co-association of *Achromobacter* and *Klebsiella* in patients with accelerated lung decline [50].

Given that COPD is a chronic inflammatory airway disease, identifying reliable biomarkers for disease endotyping, monitoring disease activity, and guiding treatment decisions remains a significant challenge. Although blood eosinophil count is widely used in clinical practice, it is limited by diurnal variability and

TABLE 1 | Investigation modalities for early COPD detection.

Modalities	Strengths	Limitations
Spirometry		
– $FEF_{25-75\%}$	– Sensitive to small airway dysfunction – Available from standard spirometry	– High variability and less reproducible – Effort- and FVC- dependence
– Z-score cut-off for FEV_1/FVC	– Enable early detection, particularly in younger patients and current smokers	– May increase complexity of interpretation
Quantitative CT		
– *Functional small airway disease* – $DPM_{AirTrap}$ – % LAA_{-856} – PRM^{fSAD}	– Quantitative assessment	– Radiation exposure – Limited accessibility – Relatively high cost
– *Emphysema* – DPM_{Emph} – % LAA_{-950} – PRM^{Emph} – HU15%		
Functional MRI		
– *Regional ventilation* – Ventilation Defect Percentage (VDP)	– Quantitative assessment – Sensitive measurement – No radiation exposure	– Limited availability – Requires specialized expertise
– *Emphysema* – Apparent Diffusion Coefficient (ADC) – Mean Diffusive Length Scale (LmD)		

Abbreviations: $\%LAA_{-950}$, percentage of low-attenuation area of the lung with attenuation values below −950 HU on full-inspiration CT; $\%LAA_{-856}$, percentage of low-attenuation area of the lung with attenuation values below −856 Hounsfield units (HU) on full-expiration CT; CT, computed tomography; $DPM_{Airtrap}$, disease probability measure-defined air trapping; DPM_{Emph}, disease probability measure-defined emphysema; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of vital capacity; HU15%, the lowest 15th percentile point of the CT lung density histogram; MRI, magnetic resonance imaging; PRM^{Emph}, parametric response mapping of emphysema; PRM^{fSAD}, parametric response of functional small airway disease.

non-specificity [51]. Fractional exhaled nitric oxide (FeNO)—an inflammatory biomarker primarily reflecting IL-13-mediated Type 2 inflammation and commonly used in asthma—has demonstrated greater temporal stability throughout the day in patients with stable COPD [52]. However, the role of FeNo as a predictive biomarker for treatment such as dupilumab, particularly in current smokers, remains to be fully elucidated. Data from BOREAS [53] and NOTUS [54] trials, which investigated the efficacy of dupilumab, showed clinical benefit regardless of baseline FeNO levels, whether above or below 20 parts per billion (ppb). These findings suggest that FeNO may not serve as a standalone predictor of treatment response in eosinophilic COPD and highlight the need for further biomarker validation.

5 | The Treatable Traits Approach in COPD

Summary

- The TT approach offers a personalised, multidimensional strategy for managing COPD by targeting traits across pulmonary, extrapulmonary, and behavioural domains.
- Extending to pre-COPD, the TT model supports early intervention based on measurable traits.

The treatable traits (TT) model represents a paradigm shift from the traditional 'one-size-fits-all' approach toward personalised, person-centred care in various respiratory diseases, including COPD. This new novel model of care uses a multidimensional assessment, identifying clinically relevant, measurable, and modifiable components of the disease. These traits, simply categorised into three primary domains: pulmonary, extrapulmonary, and behavioural/lifestyle risk factors [55] are of limited value and are just buzz words unless they are combined with appropriate biomarkers that reflect the pathobiology in individual patients. The model emphasises person-centred care and has demonstrated benefits in improving quality of life, reducing hospitalisations, and enhancing treatment precision in both asthma and COPD [56]. Figure 2 outlines a comprehensive care model, covering key elements from fundamental inhaler therapy to novel interventions such as targeted lung denervation [57, 58]. It also integrates management of extrapulmonary and behavioral factors, highlighting a holistic approach.

Recent expansions of this approach include its application to pre-COPD populations, with the goal of identifying and managing at-risk individuals prior to the development of fixed airflow limitation. This preventative strategy is supported by a gene–environment interaction framework, which emphasises early-life exposures and susceptibility. Potential targetable features in pre-COPD include symptoms, structural and physiological abnormalities, and extrapulmonary or behavioural factors

(e.g., obesity, physical inactivity, smoking, and environmental exposures) [59]. As the model is integrated into primary care and early-stage disease management, this approach provides a targeted and adaptable strategy to address COPD heterogeneity across its entire clinical spectrum.

6 | COPD Treatment

6.1 | Biological Therapy in COPD

Summary

- Dupilumab (anti-IL-4/IL-13) improved exacerbations and lung function in COPD with blood eosinophils ≥ 300 cells/μL.
- Tezepelumab showed potential in a subgroup of patients but needs further validation.
- Anti-IL-33 biologics are currently being investigated.
- Anti-IL5 (mepolizumab, benralizumab) showed modest and clinically insignificant treatment effects in large clinical trials.

Two biologic agents targeting the IL-5 pathway—mepolizumab and benralizumab—failed to meet the primary endpoint of exacerbation reduction in patients with COPD who had eosinophilia, although post hoc and pre-planned analyses showed efficacy in those with moderately raised blood eosinophil numbers. In METREX, the mepolizumab 100-mg dose did not significantly lower the annual exacerbation rate in the overall population. However, in the eosinophilic subgroup, defined by a history of eosinophils ≥ 300 cells/μL during the previous years or ≥ 150 cells/μL at screening, a modest but statistically significant 18% reduction was observed (rate ratio 0.82, $p = 0.04$). While the METREO trial, which recruited only eosinophilic patients with the same criteria but using 100- and 300-mg doses, failed to achieve significance (rate ratios 0.80, $p = 0.07$ and 0.86, $p = 0.14$, respectively). In the benralizumab trials, a blood eosinophil cutoff of ≥ 220 cells/μL was used [60]. The GALATHEA study, using the benralizumab 30- and 100-mg dose, demonstrated rate ratios of 0.96 ($p = 0.65$) and 0.83 ($p = 0.05$), respectively. A TERRANOVA study, using the benralizumab 10-, 30-, and 100-mg dose, yielded rate ratios of 0.85 ($p = 0.06$), 1.04 ($p = 0.66$), and 0.93 ($p = 0.40$), respectively, with no statistically significant reduction observed [61]. A mechanistic substudy of benralizumab in COPD showed a significant reduction of blood eosinophils, sputum eosinophils, and sputum eosinophils-derived serum mediators, without altering sputum microbiome composition or diversity [62]. In addition, a recent phase 2 study (ABRA) showed the potential role of using benralizumab (a single 100-mg dose subcutaneously) during acute exacerbation of eosinophilic airway disease, including asthma and COPD. Eligible patients had blood eosinophil counts > 250 cells/μL during the stable state and > 300 cells/μL during exacerbation. Among 158 participants, 32% had a diagnosis of COPD without asthma. The study demonstrated fewer treatment failures at 90 days in the benralizumab group (with or without concomitant prednisone) compared to the prednisone-alone group (45% vs. 74%; odds ratio 0.26; $p = 0.0005$) [63]. Both molecules are currently under investigation in large phase-3 clinical trials enriched for patients with blood eosinophils > 300 cells/μL (mepolizumab: METINEE, NCT04133909, benralizumab: RESOLUTE, NCT04053634).

Dupilumab, a monoclonal antibody (mAb) that targets IL-4 receptor alpha, thereby inhibits both IL-4 and IL-13 pathways, has demonstrated efficacy in COPD with blood eosinophils ≥ 300 cells/μL in phase 3 clinical studies—BOREAS and NOTUS [53, 54]. Administered at the same dosage used for asthma (300 mg subcutaneously every 2 weeks), dupilumab significantly reduced the annualised rate of moderate or severe exacerbations compared to placebo, with an incidence rate ratio of 0.687. Improvements in FEV_1 were observed as early as week 2, reached statistical significance by week 12, and were sustained through week 52. This rapid and sustained FEV_1 improvement suggests a potential role in mucus clearance, in addition to anti-inflammatory effects. In addition to lung function improvement, dupilumab demonstrated symptom improvement benefits. However, there was no statistically significant difference in the rate of severe exacerbations between the dupilumab and placebo groups from pooled data analysis (0.084 vs. 0.124; $p = 0.073$) [64]. The COURSE study, a phase 2a trial evaluating tezepelumab—anti-thymic stromal lymphopoietin (TSLP) mAb, used double the approved asthma dose (420 mg subcutaneous every 4 weeks) in patients with moderate to severe COPD, regardless of eosinophil count. While the study did not meet its primary endpoint of reducing moderate or severe exacerbations, a signal of efficacy was observed in the subgroup with blood eosinophils ≥ 150 cells/μL [65]. These findings highlight the importance of appropriate patient selection for biologic therapy in COPD, rather than reflecting the inherent inefficacy of the drug. Additionally, it is worth noting that the COURSE study was conducted during the COVID-19 pandemic, during which SARS-Cov-2 has been shown to disrupt airway epithelial tight junctions and alter TSLP expression, potentially confounding the observed therapeutic effects of tezepelumab. Overall, the role of tezepelumab in COPD remains to be further explored. A summary of clinical trials investigating biologic therapies for COPD is presented in Table 2.

6.2 | Smoking Cessation

Summary

- The NMR can guide individualised pharmacologic treatment.
- Both Varenicline and Cytisine have shown efficacy for smoking cessation.
- E-cigarettes offer limited benefit for nicotine abstinence and pose significant health risks.

Smoking cessation plays a crucial role in COPD management, providing mortality benefits, altering the trajectory of lung function decline, and alleviating respiratory symptoms [69]. Although several pharmacologic options are approved for smoking cessation, selecting the most appropriate therapy for each patient remains challenging. The nicotine metabolite ratio (NMR) is the ratio of trans-3-hydroxycotinine (3HC) and cotinine (COT) in blood, which represents the activity of cytochrome P450 2A6,

TABLE 2 | Biologic therapies in COPD.

Name/Mechanism	Clinical studies and criteria	Results
Mepolizumab Anti IL-5 mAb Dose: 100 or 300 mg SC q 4 wks	Phase III study (METREX, METREO) [60] Criteria: Eo ≥ 150 or ≥ 300 cells/μL	– No significant reduction in AECOPD.
Benralizumab Anti IL-5R mAb Dose: 30 mg SC q 8 wks	Phase III study (GALATHEA, TERRANOVA) [61] Criteria: Eo ≥ 220 cells/μL	– No significant reduction in AECOPD.
Dupilumab Anti IL-4Rα mAb Dose: 300 mg SC q 2 wks	Phase III study (BOREAS, NOTUS) [53, 54] Criteria: Eo ≥ 300 cells/μL	– Reduced moderate/severe AECOPD. – FEV_1 improvement.
Tezepelumab Anti TSLP mAb Dose: 420 mg SC q 4 wks	Phase IIa study (COURSE) [65] No specific Eo criteria	– No significant reduction in AECOPD.
Itepekimab Anti IL-33 mAb Dose: 300 mg SC q 2 wks	Phase IIa study [66] No specific Eo criteria	– No significant reduction in AECOPD. – Reduced AECOPD and FEV_1 improvement in former smoker subgroup.
Astegolimab Anti ST2 (IL-33 receptor) mAb Dose: 490 mg SC q 4 wks	Phase IIa study (COPD-ST2OP) [67] No specific Eo criteria	– No significant reduction in AECOPD. – Well tolerated safety profile.
Tozorakimab Anti IL-33 mAb Dose: 600 mg SC q 4 wks	Phase IIa study (FRONTIER-4) [68] No specific Eo criteria	– No significant FEV_1 improvement. – No significant reduction in COPDCompEx events. – Post-BD FEV_1 improvement in frequent exacerbator subgroup.

Abbreviations: COPDCompEx, The Chronic Obstructive Pulmonary Disease Composite Exacerbations combines exacerbations with events defined from participant e-Diaries and peak expiratory flow (PEF); Eo, Eosinophils; q, every; SC, subcutaneous; wks, weeks.

the primary enzyme for nicotine metabolism in the liver. NMR has been studied as a biomarker for optimising smoking cessation treatment [70]. Varenicline—a α4β2 nicotinic acetylcholine receptor partial agonist—demonstrated greater efficacy than bupropion in normal NMR metabolizers COPD smokers. While bupropion showed comparable efficacy in slow NMR metabolizers, it had fewer adverse effects [71]. For the patient who previously failed varenicline, continued treatment with a higher dose has been shown to increase abstinence rates. Similarly, individuals who did not respond to combination nicotine replacement therapy (NRT) may benefit from either dose escalation or switching to varenicline, both of which have been associated with improved cessation outcomes [72]. In addition, cytisine—a plant-derived partial agonist of the α4β2 nicotinic acetylcholine receptor—has demonstrated higher abstinence rates compared to usual care or NRT and comparable effectiveness to nortriptyline, with fewer reported adverse effects than varenicline. However, direct comparative data on the efficacy and safety profile of cytisine versus varenicline remain limited and merit further study [73–75]. E-cigarettes were proposed as an alternative option for nicotine addiction therapy. One study reported a 28.9% abstinence rate from tobacco smoking in the e-cigarette group compared to 16.3% in the control group. However, when considering complete nicotine abstinence, the rate was lower in the e-cigarette group (20.1%) than in the control group (33.7%) [76]. These raise concerns about continued nicotine dependence as well as health risks of e-cigarettes, including e-cigarette or vaping product use-associated lung injury (EVALI), cytotoxicity and DNA damage to airway epithelial cells, increased airway inflammation, and decreased mucociliary clearance [77]. The use of e-cigarettes for smoking cessation remains controversial, as the potential risks outweigh the benefits; moreover, efforts to promote vaping cessation should be further strengthened. There is also evidence supporting the use of varenicline for vaping cessation [78, 79].

6.3 | Mood Disorder Management

Summary

- Negative mood states can amplify the perception of dyspnoea, creating a vicious cycle.
- Self-management strategies are essential, while pharmacologic options remain limited.

COPD is well recognised to be associated with an increased risk of depression. An observational study using bidirectional Mendelian randomization analysis identified depression as a potential causal contributor to morbidity in patients with COPD [80]. Negative mood states have also been shown to influence the perception of dyspnoea. Participants exposed to negative emotional visual stimuli reported higher dyspnoea intensity scores during exercise testing compared to neutral or positive stimuli [81]. Contrariwise, breathlessness symptoms can be attributed to unfavourable emotional experiences, including panic attacks, thereby propagating the vicious cycle between dyspnoea perception and mood disturbance. Proactive self-management

strategies will help patients break this cycle and reduce the psychological amplification of respiratory symptoms [82]. There has also been interest in treating dyspnoea with antidepressants. However, the BETTER-B trial, a Phase 3 randomised controlled study evaluating mirtazapine (15–45 mg orally) for severe breathlessness, found no significant improvement in dyspnoea compared to placebo [83].

6.4 | Pulmonary Rehabilitation

Summary

- PR benefits in both AECOPD and stable COPD.
- Post-BLVR-EBV patients benefit from continued PR.

Pulmonary rehabilitation (PR) is well known for its benefits, including reduced dyspnoea, enhanced exercise capacity, and improved quality of life, achieved through improved oxygen utilisation, mitochondrial function in skeletal muscles, and enhanced airway mucus clearance. Among patients with acute exacerbations of COPD (AECOPD), PR has been shown to reduce hospital readmissions and improve submaximal cardiovascular performance [84]. In ex-smokers with stable COPD, an 8-week PR program was associated with a reduction in cardiovascular risk [85].

Bronchoscopic lung volume reduction with endo-bronchial valves (BLVR-EBV) is an interventional treatment designed to reduce pulmonary hyperinflation in emphysematous patients and thereby improve ventilation efficiency. Both PR and BLVR-EBV have demonstrated benefits in selected patient populations. A randomised controlled trial assessing the combined effect of these modalities used constant work rate cycle test endurance time as the primary endpoint. The results showed a modest improvement in endurance time among patients who received PR following BLVR-EBV [86]. This finding should not be interpreted as a diminished value of PR. Rather, the specific disease phenotype of patients selected for BLVR-EBV may explain the attenuated response. These findings underscore the importance of continuing PR post-BLVR-EBV and support the recommendation to encourage PR participation in the subgroup of patients [87].

6.5 | Long-Term Domiciliary Oxygen Therapy

Summary

- LTDOT could provide benefit in patients with early exertional desaturation.

Long-term domiciliary oxygen therapy (LTDOT)—oxygen use for more than 15 h per day—has documented a survival benefit for patients with severe resting hypoxemia (partial pressure of oxygen in the arterial blood (PaO_2) ≤ 55 mmHg) but not in the mild to moderate hypoxemia or nocturnal desaturation group [88]. A recent post hoc analysis provided intriguing data suggesting a potential survival advantage of LTDOT in patients with early desaturation during the 6-min walk test, defined as oxygen saturation < 88% within the first minute. Over a mean follow-up of 4.48 ± 2.97 years, survival in the LTDOT group was 76%, compared to 11% in the non-LTDOT group, with mean survival times of 11.83 ± 1.12 years versus 4.24 ± 0.39 years, respectively. These findings must be viewed in the context of their methodological limitations as they stem from a subgroup analysis of a study not originally designed to test this hypothesis. Prospective, well-controlled studies are needed to validate these results [89].

7 | Comorbidities in COPD

Summary

- Increased CVS risk in COPD is observed across COPD phenotypes.
- OSA and nocturnal hypoxemia are prevalent and linked to mortality; screening is essential.
- Obesity and physical inactivity are related to lower lung function and AECOPD.
- Dysfunctional breathing is common but under recognized in COPD; it may worsen dyspnoea and represents a treatable trait.

Although COPD is primarily a disease of airway inflammation, the inflammatory process extends beyond the lungs. Its systemic nature contributes to a shared pathogenesis with cardiovascular diseases, increasing the risk of conditions such as ischemic heart disease, heart failure, and stroke. This elevated cardiovascular risk has been observed across all COPD phenotypes—chronic bronchitis, emphysema, and combined phenotypes—with reported odds ratios of 1.76, 2.31, and 2.98, respectively, compared to individuals without COPD [90]. These findings underscore the importance of cardiovascular screening in COPD, which remains challenging due to the overlap and masking of symptoms. The particularly elevated risk in patients with the combined phenotype suggests the involvement of multiple underlying mechanisms, highlighting the need for a better understanding of COPD endotypes and phenotypes [91].

Sleep-disordered breathing is also prevalent in COPD and has been linked to increased cardiovascular risk. The prevalence of obstructive sleep apnoea (OSA) in COPD is approximately 32% and is independently associated with obesity (BMI ≥ 30 kg/m^2) and severe AECOPD. On the other hand, nocturnal hypoxemia without OSA or isolated nocturnal hypoxemia prevalence is 27%, associated with lower FEV_1 and lower resting oxygen saturation. If left untreated, COPD-OSA overlap syndrome is associated with a higher risk of mortality (hazard ratio 1.74) and increased exacerbation frequency [92]. Given these risks, overnight oxygen saturation monitoring or polysomnography should be considered, particularly in high-risk groups such as those with obesity. Obesity itself is independently associated with reduced lung function. Higher BMI from early adulthood correlates with lower FEV_1 and FVC, and in women, is also associated with a lower FEV_1/FVC ratio, indicating a potential link

to airflow obstruction. In contrast, physical activity is positively associated with better lung function [93]. Therefore, promoting weight loss and encouraging physical activity during adulthood may represent preventive strategies to reduce the future burden of COPD [94].

Dysfunctional breathing, or breathing pattern disorder, is a clinical conundrum with notable prevalence among patients with COPD. It is characterised by abnormal breathing patterns, such as hyperventilation, periodic sighing, upper thoracic breathing, and breathing asynchrony—often coexisting within the same individual. Although frequently overlooked, dysfunctional breathing is increasingly recognised as a treatable trait that may contribute to unexplained or disproportionate breathlessness, even in the presence of confirmed respiratory disease [95]. Based on the Nijmegan questionnaire for dysfunctional breathing [96], one cohort study reported almost 50% prevalence among COPD patients attending a tertiary care teaching clinic [97].

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Conflicts of Interest

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